Access DB# 123401

# SEARCH REQUEST FORM

**Scientific and Technical Information Center**

Requester's Full Name: S. Kumar Examiner #: 64594 Date: 6/1/04
Art Unit: 1621 Phone Number 272-0640 Serial Number: 10/606403
Mail Box and Bldg/Room Location: REM 5D61 5C18 Results Format Preferred (circle): PAPER DISK E-MAIL

**If more than one search is submitted, please prioritize searches in order of need.**

**********

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Novel process for preparing and isolating racbicalutamide

Inventors (please provide full names): Ber-Zion Dolitzky et al

Earliest Priority Filing Date: 6/13/2001

WHAT IS CLAIMED IS:

1. A process for the purification and isolation of bicalutamide by solution crystallization, comprising the steps of:
(i) combining crude bicalutamide and a solvent;
(ii) crystallizing the bicalutamide from the solvent; and
(iii) collecting the crystals of bicalutamide.

2. The process of claim 1, wherein the the crystallizing step (ii) comprises seeding the bicalutamide suspension.

3. The process of claim 1, further comprising heating the resulting bicalutamide solution to about the boiling point of the solvent.

4. The process of claim 1, wherein the solvent is selected from the group consisting of water, methanol, ethanol, DCM, toluene, PE, chloroform, hexane, 1,2-dichloroethane, diethyl ether, propanol and isopropanol.

5. The process of claim 1, wherein the solvent is selected from the group consisting of ethanol, propanol and isopropanol.

6. A process for the purification and isolation of bicalutamide by solution crystallization, comprising the steps of:
(i) combining crude bicalutamide and a first solvent;
(ii) adding a second solvent to the crude bicalutamide-first solvent mixture;
(iii) crystallizing the bicalutamide from the solvents; and
(iv) collecting the crystals of bicalutamide.

6/2/04

7. The process of claim 6, further comprising heating the bicalutamide solution of step (i) to about the boiling point of the solvent.

# STIC Search Report
## Biotech-Chem Library

## STIC Database Tracking Number: 123401

| | |
|---|---|
| **TO: Shailendra Kumar**<br>**Location: 5d61 / 5c18**<br>**Wednesday, June 02, 2004**<br>**Art Unit: 1621**<br>**Phone: 272-0640**<br>**Serial Number: 10 / 606403** | **From: Jan Delaval**<br>**Location: Biotech-Chem Library**<br>**Rem 1A51**<br>**Phone: 272-2504**<br><br>**jan.delaval@uspto.gov** |

## Search Notes

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=> fil reg
FILE 'REGISTRY' ENTERED AT 10:06:25 ON 02 JUN 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:     1 JUN 2004  HIGHEST RN 688308-86-3
DICTIONARY FILE UPDATES:    1 JUN 2004  HIGHEST RN 688308-86-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l6

L6   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   113299-40-4  REGISTRY
CN   Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
     fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI)   (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-
     fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (R)-
OTHER NAMES:
CN   (R)-Bicalutamide
CN   (R)-Casodex
FS   STEREOSEARCH
MF   C18 H14 F4 N2 O4 S
SR   CA
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, IMSPATENTS,
       IMSRESEARCH, PS, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); PROC
       (Process); PRP (Properties); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); FORM (Formation, nonpreparative); PREP (Preparation); PROC
       (Process); USES (Uses)

Absolute stereochemistry.  Rotation (-).
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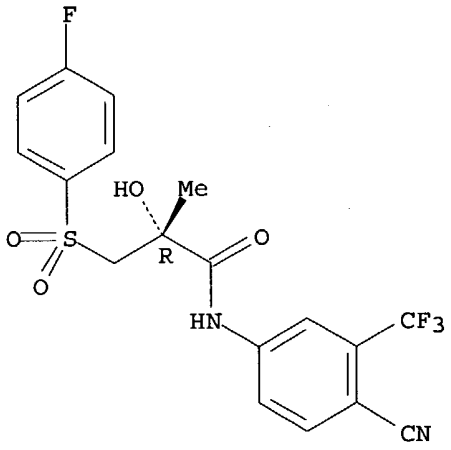



**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

24 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:303414

REFERENCE 2: 139:375064

REFERENCE 3: 138:406952

REFERENCE 4: 138:343868

REFERENCE 5: 138:321017

REFERENCE 6: 138:24551

REFERENCE 7: 137:384623

REFERENCE 8: 137:284397

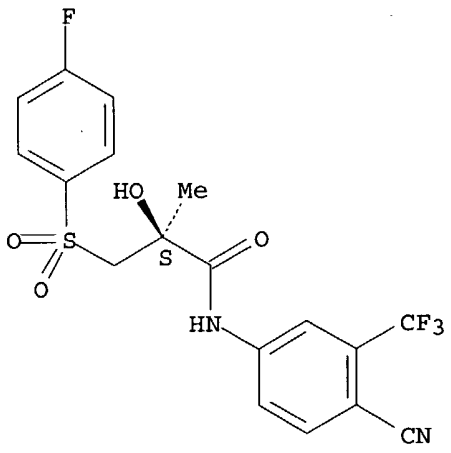
REFERENCE 9: 136:79780

REFERENCE 10: 135:313717

L6 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 113299-38-0 REGISTRY
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (S)-
OTHER NAMES:
CN **(S)-Casodex**
FS STEREOSEARCH
MF **C18 H14 F4 N2 O4 S**
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, IMSPATENTS, IMSRESEARCH, PS, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

Absolute stereochemistry. Rotation (+).

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13 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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REFERENCE 2: 137:384623

REFERENCE 3: 136:79780

REFERENCE 4: 134:326279

REFERENCE 5: 134:86040

REFERENCE 6: 133:12739

REFERENCE 7: 130:49289

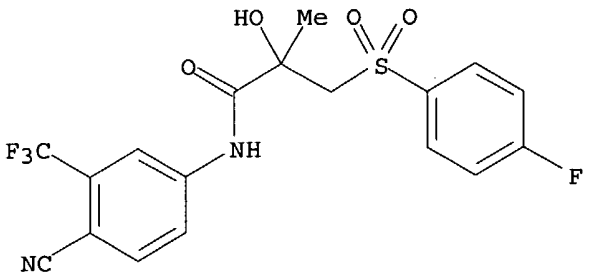
REFERENCE 8: 127:242768

REFERENCE 9: 124:306528

REFERENCE 10: 123:160082

L6 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 90357-06-5 REGISTRY
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (±)-
OTHER NAMES:
CN (±)-4'-Cyano-α,α,α-trifluoro-3-[(p-fluorophenyl)sulfonyl]-2-methyl-m-lactotoluidide
CN **Bicalutamide**
CN **Casodex**

CN Cosudex
CN ICI 176334
CN ZD 176334
DR 151262-58-7
MF C18 H14 F4 N2 O4 S
LC STN Files: ADISINSIGHT, ADISNEWS, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO
DT.CA CAplus document type: Conference; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

358 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
359 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:368658

REFERENCE 2: 140:350595

REFERENCE 3: 140:332704

REFERENCE 4: 140:321363

REFERENCE 5: 140:315331

REFERENCE 6: 140:303414

REFERENCE 7: 140:292649

REFERENCE 8: 140:280889

REFERENCE 9: 140:270600

REFERENCE 10: 140:264968

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L1             1 S E3
               E BICALUTAMIDE
L2             3 S E3,L1
               E C18H14F4N2O4S/MF
L3             4 S E3 NOT L2
L4             1 S L3 AND 2/NR
L5             4 S L1,L2,L4
L6             3 S L5 AND CASODEX
               SEL RN
L7             0 S E1-E3/CRN

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L8           369 S L6
L9           459 S CASODEX OR BICALUTAMIDE OR COSUDEX OR ICI176334 OR ZD167334 O
L10          469 S L8,L9
L11          316 S L10 AND (PD<=20010613 OR PRD<=20010613 OR AD<=20010613)
L12            2 S (US20040044249 OR US6737550)/PN OR (WO2002-US18329 OR US2002-
               E DOLITZKY B/AU
L13           28 S E4
               E REANY OF/AU
L14            9 S E3,E4
               E SHAMMAI J/AU
L15            2 S E4
               E BIOGAL/PA,CS
L16          349 S E3-E43
               E TEVA/PA,CS
L17          239 S E3-E75
               E SHAMAI J/AU
L18            1 S E4
L19            2 S L10 AND L12-L18
               E CRYSTAL/CT
L20            0 S E59-E61 AND L10
L21            0 S E64+OLD,NT,PFT AND L10
L22            0 S E103,E106 AND L10
L23            1 S E114+OLD,NT,PFT AND L10
L24            0 S E131+OLD,NT,PFT AND L10
L25            3 S E141+OLD,NT,PFT AND L10
L26            0 S E161+OLD,NT,PFT AND L10
L27            0 S E187 AND L10
L28            0 S E190+OLD,NT,PFT AND L10
L29            0 S E265+OLD,NT,PFT AND L10
L30            0 S E269+OLD,NT,PFT AND L10
L31            2 S E304+OLD,NT,PFT AND L10
L32            0 S E342+OLD,NT,PFT AND L10
L33            0 S E345+OLD,NT,PFT AND L10
L34            0 S E370+OLD,NT,PFT AND L10
               E E304+ALL
L35            0 S L10 AND (E21+OLD,NT,PFT OR E22+OLD,NT,PFT OR E23+OLD,NT,PFT O
L36            0 S L10 AND E27+OLD,NT,PFT
L37           10 S L10 AND ?CRYS?
L38            1 S L10 AND CRYS?/SC,SX
L39           10 S L23,L25,L31,L37,L38
L40            4 S L39 AND L11
L41            3 S L6 (L) (PREP+NT OR PROC+NT)/RL AND L40
L42            1 S L41 AND PREPARATION/TI
L43            2 S L19,L42
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L44           1 S ETHYL 2 4 FLUOROPHENYL SULFONE 2 HYDROXY PROPION?
L45           2 S L43,L44
                SEL RN

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L46          40 S E1-E40
L47           3 S L46 AND L6
L48          11 S 110-54-3 OR 108-88-3 OR 67-66-3 OR 67-63-0 OR 67-56-1 OR 64-1
L49           7 S 108-10-1 OR 67-68-5 OR 109-99-9 OR 141-78-6 OR 75-05-8 OR 67-
L50           1 S 109-72-8
L51          18 S L46 NOT L47-L50
L52           2 S L51 AND C8H5F3N2
L53          16 S L51 NOT L52
L54           1 S L53 AND C10H11FO3S
L55           1 S L53 AND C12H15FO5S
L56          14 S L53 NOT L54,L55

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L57          15 S L10 AND L48
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L59          14 S L10 AND L52
L60           3 S L10 AND L50
L61           4 S L10 AND L54,L55
L62          20 S L11 AND L57-L61
L63          10 S L8(L)PREP+NT/RL AND L62
L64           1 S L8(L)PROC+NT/RL AND L62
L65           2 S L45 AND L62-L64
L66           8 S L63,L64 NOT L65
L67          11 S L6 (L) PREP+NT/RL AND L11
L68          29 S L6 (L) PROC+NT/RL AND L11
L69           1 S L67 NOT L65,L66
L70          28 S L68 NOT L66,L67
L71          10 S L65,L66 AND L8-L45,L57-L70

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                E BICALUTAMIDE/DCN
                E CASODEX/DCN
                E R04776+ALL/DCN
                E RA1M70+ALL/DCN
                E BICALUTAMIDE/CN
L73           1 S E3
L74           1 S RA1M70/DCN
L75         123 S L72,L74
                E BICALUTAM
L76          94 S E4-E6
                E BICALUTAM/ABEX
L77          25 S E4
                E CASODEX/BIX
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L78          31 S E3,E4
L79         124 S L75-L78
L80          12 S L79 AND ?CRYS?/BIX
                SEL DN AN 4-7 11 12
L81           6 S L80 NOT E1-E12
L82           1 S L12
                E BIOGAL/PA
L83         221 S E3-E11
                E TEVA/PA
L84         238 S E3-E20
                E DOLITZKY B/AU
L85          28 S E3,E4
                E REANY O/AU
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L86             2 S E3
                  E SHAMMAI J/AU
L87             2 S E3
                  E SHAMAI J/AU
L88             1 S E3
L89             1 S L79 AND L83-L88
L90             7 S L82,L89,L81
                  E RA37J7+ALL/DCN
L91             9 S L79 AND C07C315/IC,ICM,ICS
L92            10 S L90,L91 AND L72-L91

     FILE 'REGISTRY' ENTERED AT 10:06:25 ON 02 JUN 2004

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 10:06:39 ON 02 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 2 Jun 2004  VOL 140 ISS 23
FILE LAST UPDATED: 1 Jun 2004  (20040601/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d l71 all hitstr tot

L71  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2004:182593  HCAPLUS
DN   140:235504
ED   Entered STN:  05 Mar 2004
TI   Preparation and crystallization of
     bicalutamide
IN   Dolitzky, Ben-Zion; Reany, Ofer; Shammai,
     Jenny
PA   Israel
SO   U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No. 170,721.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  C07C317-28
NCL  564162000
CC   25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
     Section cross-reference(s): 63
FAN.CNT 2
     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
PI   US 2004044249      A1   20040304      US 2003-606403   20030625 <--
     US 2003045741      A1   20030306      US 2002-170721   20020613 <--
     US 6737550         B2   20040518
     US 2004059147      A1   20040325      US 2003-668982   20030922 <--
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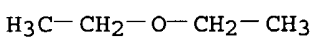
PRAI US 2001-298009P P 20010613 <--
US 2002-371069P P 20020409 <--
US 2002-170721 A2 20020613
OS CASREACT 140:235504
AB Racemic N-[4-cyano-3-trifluoromethylphenyl]-3-[4-fluorophenylsulfonyl]-2-hydroxy-2-methylpropionamide (**bicalutamide**) was prepared starting from Et pyruvate and Me methacrylate. Thus, 5-amino-2-cyanobenzotrifluoride was treated with DABCO and reacted with deprotonated Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate (prepared from Et pyruvate) to give 40% **bicalutamide.** Micronized particles of **bicalutamide** can be obtained as pharmaceutical compns. that are useful for its anti-androgen activity (no data). **Bicalutamide** intermediates were also prepared, including Et 2-(4-fluorophenylsulfonyl)-2-hydroxy-2-methylpropionate, Me 2,3-epoxy-2-methylpropionate and 2-hydroxy-2-methyl-3-(4-fluorophenylthio)propionic acid. The present invention further discloses the isolation and purification of **bicalutamide** by various **crystallization** methods.
ST **bicalutamide** prepn **crystn** micronization; cyanophenyl fluorophenylsulfonyl hydroxy propionamide prepn **crystn** micronization
IT Ligroine
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)
IT Drug delivery systems
(microparticles; preparation, micronization and **crystallization** of **bicalutamide**)
IT **Crystallization**
(preparation, micronization and **crystallization** of **bicalutamide**)
IT **60-29-7**, Diethyl ether, uses **64-17-5**, Ethanol, uses **67-56-1**, Methanol, uses **67-63-0**, Isopropanol, uses **67-64-1**, Acetone, uses **67-66-3**, Chloroform, uses **67-68-5**, DMSO, uses **68-12-2**, DMF, uses **71-23-8**, Propanol, uses **75-05-8**, Acetonitrile, uses **75-09-2**, Dichloromethane, uses **107-06-2**, 1,2-Dichloroethane, uses **108-10-1**, Isobutyl methyl ketone **108-88-3**, Toluene, uses **109-99-9**, THF, uses **110-54-3**, Hexane, uses **141-78-6**, Ethyl acetate, uses **7732-18-5**, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)
IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)**
(preparation, micronization and **crystallization** of **bicalutamide**)
IT 80-62-6, Methyl methacrylate 371-42-6, 4-Fluorothiophenol 455-15-2, 4-Fluorophenyl methyl sulfone 617-35-6, Ethyl pyruvate **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)
IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate **339530-91-5P** **478190-74-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)
IT **60-29-7**, Diethyl ether, uses **64-17-5**, Ethanol, uses **67-56-1**, Methanol, uses **67-63-0**, Isopropanol, uses **67-64-1**, Acetone, uses **67-66-3**, Chloroform, uses **67-68-5**, DMSO, uses **68-12-2**, DMF, uses **71-23-8**, Propanol, uses **75-05-8**, Acetonitrile, uses **75-09-2**, Dichloromethane, uses **107-06-2**, 1,2-Dichloroethane, uses

**108-10-1**, Isobutyl methyl ketone **108-88-3**, Toluene, uses
**109-99-9**, THF, uses **110-54-3**, Hexane, uses
**141-78-6**, Ethyl acetate, uses **7732-18-5**, Water, uses
RL: NUU (Other use, unclassified); USES (Uses)
(**crystallization** solvent; preparation, micronization and **crystallization** of **bicalutamide**)

RN 60-29-7 HCAPLUS
CN Ethane, 1,1'-oxybis- (9CI) (CA INDEX NAME)



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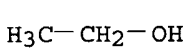

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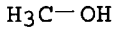

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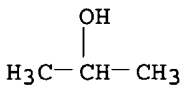

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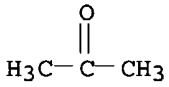
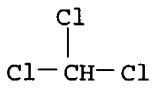
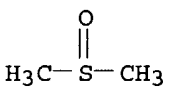
CN 2-Propanone (9CI) (CA INDEX NAME)



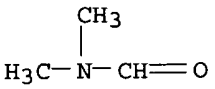
RN 67-66-3 HCAPLUS
CN Methane, trichloro- (9CI) (CA INDEX NAME)



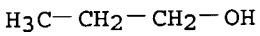
RN 67-68-5 HCAPLUS
CN Methane, sulfinylbis- (9CI) (CA INDEX NAME)



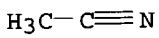
RN 68-12-2 HCAPLUS
CN Formamide, N,N-dimethyl- (8CI, 9CI) (CA INDEX NAME)



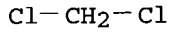
RN 71-23-8 HCAPLUS
CN 1-Propanol (9CI) (CA INDEX NAME)



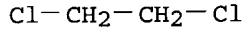
RN 75-05-8 HCAPLUS
CN Acetonitrile (8CI, 9CI) (CA INDEX NAME)



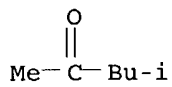
RN 75-09-2 HCAPLUS
CN Methane, dichloro- (8CI, 9CI) (CA INDEX NAME)



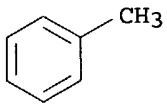
RN 107-06-2 HCAPLUS
CN Ethane, 1,2-dichloro- (8CI, 9CI) (CA INDEX NAME)



RN 108-10-1 HCAPLUS
CN 2-Pentanone, 4-methyl- (7CI, 8CI, 9CI) (CA INDEX NAME)



RN 108-88-3 HCAPLUS
CN Benzene, methyl- (9CI) (CA INDEX NAME)



RN 109-99-9 HCAPLUS
CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)

RN 110-54-3 HCAPLUS
CN Hexane (8CI, 9CI) (CA INDEX NAME)

Me—$(CH_2)_4$—Me

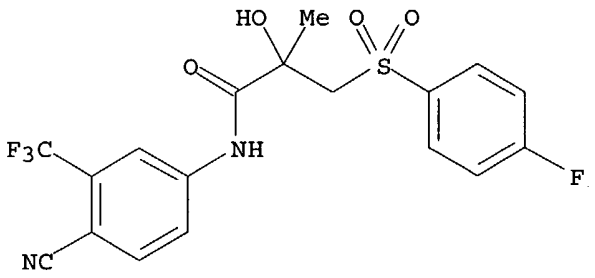
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

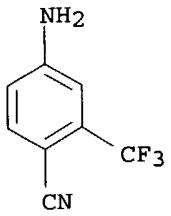
RN 7732-18-5 HCAPLUS
CN Water (8CI, 9CI) (CA INDEX NAME)

$H_2O$

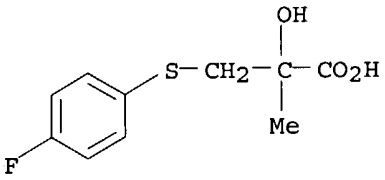
IT **90357-06-5P, Bicalutamide**
RL: **PEP (Physical, engineering or chemical process); PUR (Purification or recovery); PYP (Physical process); SPN (Synthetic preparation); PREP (Preparation); PROC (Process)**
(preparation, micronization and **crystallization** of **bicalutamide**)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



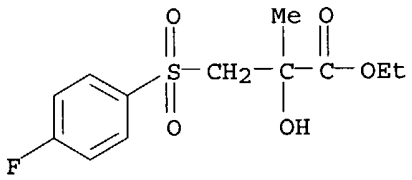

IT **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



IT **339530-91-5P 478190-74-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, micronization and **crystallization** of **bicalutamide**)
RN 339530-91-5 HCAPLUS
CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 478190-74-8 HCAPLUS
CN Propanoic acid, 3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, ethyl ester (9CI) (CA INDEX NAME)



L71 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:964133 HCAPLUS
DN 138:24551
ED Entered STN: 20 Dec 2002
TI Preparation of rac-**bicalutamide**
IN **Dolitzky, Ben-Zion; Reany, Ofer; Shamai, Jenny**
PA **Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.; Biogal Gyogyszergyar**
SO PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 63
FAN.CNT 2

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002100339 | A2 | 20021219 | WO 2002-US18329 | 20020613 <-- |
| | WO 2002100339 | A3 | 20031016 | | |

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1406855 A2 20040414 EP 2002-739801 20020613 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI US 2001-298009P P 20010613 <--

US 2002-371069P P 20020409 <--

WO 2002-US18329 W 20020613 <--

OS CASREACT 138:24551

AB Racemic and optically active N-[4-cyano-3-trifluoromethylphenyl]-3-[4-fluorophenylsulfonyl]-2-hydroxy-2-Me propionamide (**bicalutamide**) were prepared starting from Et pyruvate and Me methacrylate. Thus, 5-amino-2-cyanobenzotrifluoride was treated with DABCO and reacted with deprotonated **ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy propionate** (prepared from Et pyruvate) to give %40 rac-**bicalutamide.** Micronized particles of rac-**bicalutamide** can be obtained as pharmaceutical compns. that are useful for its anti-androgen activity (no data). **Bicalutamide** intermediates were also prepared, including **ethyl-[2-(4-fluorophenyl sulfone)]-2-hydroxy propionate**, 1,2-epoxy-2-Me propionate and 2-hydroxy-2-methyl-3-(4-fluorophenylthio) propionic acid.

ST **bicalutamide** prepn; cyanotrifluoromethylphenylfluorophenylsulfon ylhydroxymethylpropionamide prepn

IT 280-57-9, DABCO
RL: RGT (Reagent); RACT (Reactant or reagent)
(anion stabilizer; preparation of rac-**bicalutamide**)

IT **109-72-8**, Butyl lithium, reactions 1310-58-3, Potassium hydroxide, reactions 1310-73-2, Sodium hydroxide, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; preparation of rac-**bicalutamide**)

IT **67-66-3**, Chloroform, uses
RL: NUU (Other use, unclassified); USES (Uses)
(extraction with; preparation of rac-**bicalutamide**)

IT 7727-37-9, Nitrogen, uses
RL: NUU (Other use, unclassified); USES (Uses)
(inert atmospheric; preparation of rac-**bicalutamide**)

IT 478190-75-9 **478190-76-0**
RL: FMU (Formation, unclassified); RCT (Reactant); FORM (Formation, nonpreparative); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)

IT **141-78-6**, Ethyl acetate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of rac-**bicalutamide**)

IT 80-62-6, Methyl methacrylate 371-42-6, 4-Fluorothiophenol 455-15-2, 4-Fluorophenyl methyl sulfone 617-35-6, Ethyl pyruvate **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline 37222-66-5, Oxone
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)

IT 58653-97-7P, Methyl 2-methyl-2-oxiranecarboxylate **339530-91-5P** **478190-74-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)

IT 7647-01-0, Hydrochloric acid, reactions 7664-38-2, Phosphoric acid,

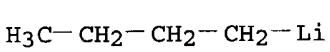
reactions 7697-37-2, Nitric acid, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)

IT **90357-06-5P**, **Bicalutamide 113299-38-0P**
**113299-40-4P**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(preparation of rac-**bicalutamide**)

IT **60-29-7**, Diethyl ether, uses **67-56-1**, Methanol, uses
**109-99-9**, THF, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; preparation of rac-**bicalutamide**)

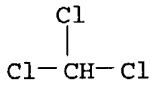
IT **109-72-8**, Butyl lithium, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; preparation of rac-**bicalutamide**)

RN 109-72-8 HCAPLUS
CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)



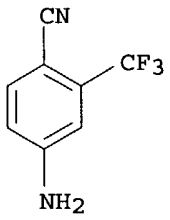
IT **67-66-3**, Chloroform, uses
RL: NUU (Other use, unclassified); USES (Uses)
(extraction with; preparation of rac-**bicalutamide**)

RN 67-66-3 HCAPLUS
CN Methane, trichloro- (9CI) (CA INDEX NAME)



IT **478190-76-0**
RL: FMU (Formation, unclassified); RCT (Reactant); FORM (Formation, nonpreparative); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)

RN 478190-76-0 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)-, monolithium salt (9CI) (CA INDEX NAME)

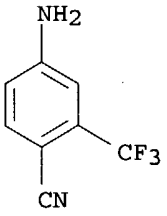


IT **141-78-6**, Ethyl acetate, uses
RL: NUU (Other use, unclassified); USES (Uses)
(preparation of rac-**bicalutamide**)

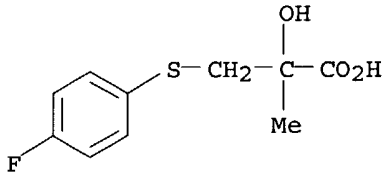
RN 141-78-6 HCAPLUS
CN Acetic acid ethyl ester (8CI, 9CI) (CA INDEX NAME)

Et—O—Ac

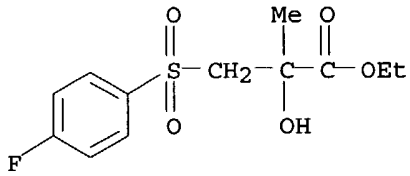
IT **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



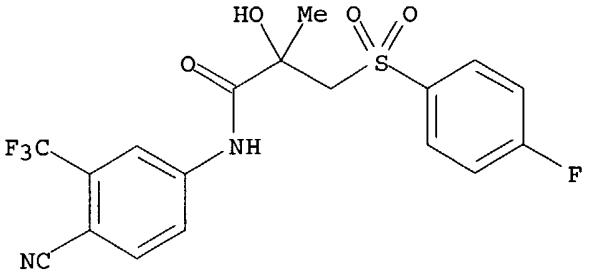
IT **339530-91-5P 478190-74-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of rac-**bicalutamide**)
RN 339530-91-5 HCAPLUS
CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



RN 478190-74-8 HCAPLUS
CN Propanoic acid, 3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, ethyl ester (9CI) (CA INDEX NAME)

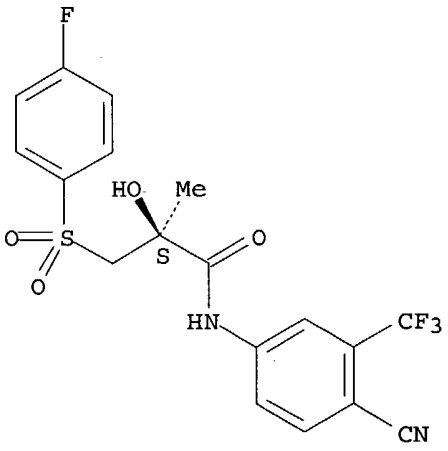


IT **90357-06-5P, Bicalutamide 113299-38-0P**
**113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation of rac-**bicalutamide**)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



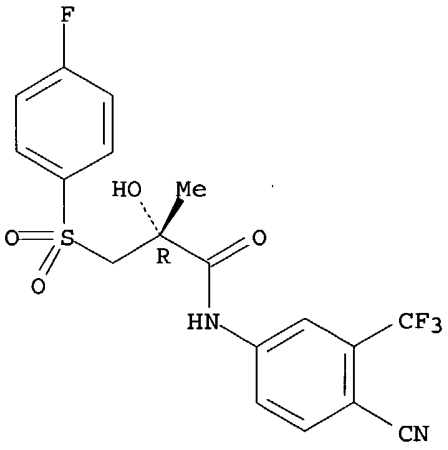
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **60-29-7**, Diethyl ether, uses **67-56-1**, Methanol, uses **109-99-9**, THF, uses

RL: NUU (Other use, unclassified); USES (Uses)
(solvent; preparation of rac-**bicalutamide**)
RN 60-29-7 HCAPLUS
CN Ethane, 1,1'-oxybis- (9CI) (CA INDEX NAME)

$H_3C-CH_2-O-CH_2-CH_3$

RN 67-56-1 HCAPLUS
CN Methanol (8CI, 9CI) (CA INDEX NAME)

$H_3C-OH$

RN 109-99-9 HCAPLUS
CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)

L71 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:850359 HCAPLUS
DN 137:337686
ED Entered STN: 08 Nov 2002
TI Preparation of acylanilide derivatives and **bicalutamide** via amidation and alkylation
IN Ekwuribe, Nnochiri N.; James, Kenneth D.
PA USA
SO U.S. Pat. Appl. Publ., 12 pp.
CODEN: USXXCO
DT Patent
LA English
IC ICM C07C255-49
ICS C07C235-32
NCL 558418000
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 2002165406 | A1 | 20021107 | US 2001-847229 | 20010502 <-- |
| | US 6479692 | B1 | 20021112 | | |
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| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| | EP 1383735 | A1 | 20040128 | EP 2002-734091 | 20020502 <-- |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| | US 2003045742 | A1 | 20030306 | US 2002-268155 | 20021010 <-- |
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WO 2002-US13591 W 20020502
OS CASREACT 137:337686; MARPAT 137:337686
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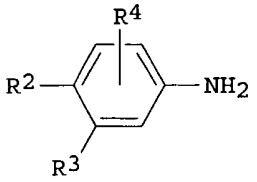


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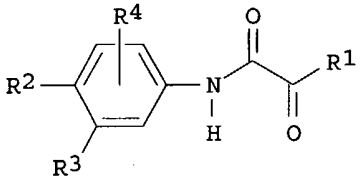
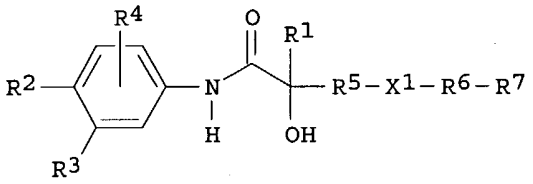



II




III

AB The method of preparation for acylanilides, including **bicalutamide**, is outlined under various conditions using carboxylic acid halogenating compds. in the amidation step and organometallic agents in the alkylation step. The acylanilides were prepared by reacting oxocarboxylic acids R1COCO2H (R1 = alkyl, haloalkyl) with anilines I (R2 = cyano, NO2, Ph, etc., R3 = F, alkylsulfinyl, PhS, etc., R4 = H, halogen), which gave the corresponding amides II. The intermediate amides were then alkylated with R5-X1-R6-R7 (R5 = unsubstituted or substituted alkyl up to 6 carbons, R6 = direct link or unsubstituted or substituted alkyl up to 6 carbons, R7 = alkyl, alkenyl, cycloalkyl, etc., X1 = O, S, SO2, etc.) to give the final acylanilide derivs. III. **Bicalutamide** was synthesized using this method by treating pyruvic acid with COCl2 and 4-cyano-3-(trifluoromethyl)aniline to give N-[4-cyano-3-(trifluoromethyl)phenyl]-2-oxopropionamide, which was then alkylated with 4-trifluorophenyl Me sulfone after treatment with BuLi.

ST **bicalutamide** prepn; acylanilide prepn; alkylation acylanilide prepn; amidation acylanilide prepn; anilide acyl prepn

IT Anilides
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(acyl; preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT Alkylation
Amidation
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT 87310-69-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

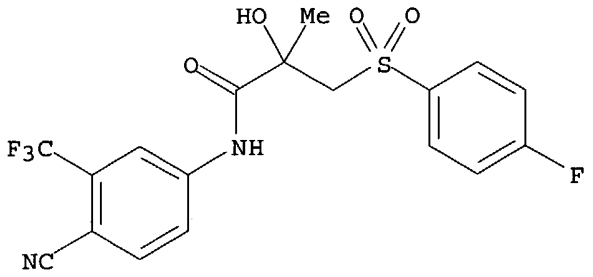
IT 127-17-3, Pyruvic acid, reactions 455-15-2 **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

IT **109-72-8**, Butyllithium, reactions 507-16-4, Thionyl bromide 7719-09-7, Thionyl chloride
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

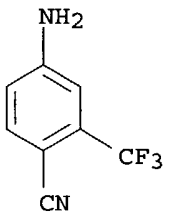
IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



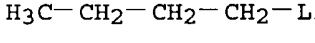

IT **654-70-6**, 4-Cyano-3-(trifluoromethyl)aniline
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)




IT **109-72-8**, Butyllithium, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(preparation of acylanilides and **bicalutamide** via amidation and alkylation)

RN 109-72-8 HCAPLUS
CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)




L71 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:240719 HCAPLUS
DN 136:262992

ED Entered STN: 28 Mar 2002
TI Process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compounds
IN Chen, Bang-Chi; Sundeen, Joseph E.; Zhao, Rulin
PA Bristol-Myers Squibb Company, USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C317-46
ICS C07C315-02; C07C323-62; C07C319-14; C07D303-48; C07D301-16; C07C255-66; C07C253-30; C07C231-08
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 45
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2002024638 | A1 | 20020328 | WO 2001-US42171 | 20010917 <-- |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002086902 | A1 | 20020704 | US 2001-953759 | 20010917 <-- |
| US 6562994 | B2 | 20030513 | | |
| EP 1322603 | A1 | 20030702 | EP 2001-975752 | 20010917 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004509164 | T2 | 20040325 | JP 2002-529051 | 20010917 <-- |
| PRAI US 2000-234121P | P | 20000921 <-- | | |
| WO 2001-US42171 | W | 20010917 | | |

OS CASREACT 136:262992; MARPAT 136:262992
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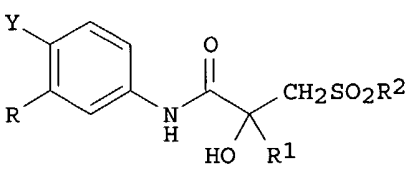

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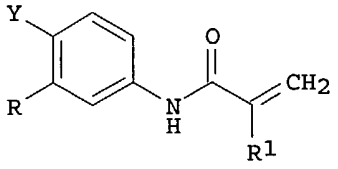

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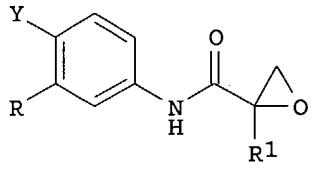
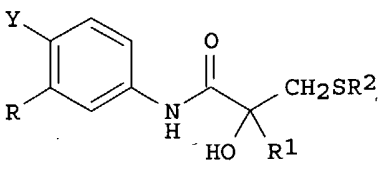


III



IV

AB The title compds. [I; Y = cyano, nitro, perfluoroalkyl, alkylcarbonyl,

alkoxycarbonyl, alkylsulfonyl; R = perfluoroalkyl, cyano, nitro, alkylcarbonyl, alkoxycarbonyl, alkyl, alkoxy; R1 = (halo)alkyl; R2 = alkyl, aryl, heteroaryl; e.g., **bicalutamide**], useful for the treatment of androgen-mediated diseases (no data), are prepared without the use of chromatog. sepns. and expensive starting materials by phenylating propenamides H2NCOC(R1):CH2 (e.g., methacrylamide) with leaving group-substituted benzenes 1,2,4-C6H3Y(R)X (X = F, Cl, Br, I, SO3R3; R3 = alkyl, aryl; e.g., 4-fluoro-2-trifluoromethylbenzonitrile) so as to form a N-phenyl-substituted propenamides [II; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]methacrylamide] which are then oxidized into the corresponding epoxides [III; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]methacrylamide epoxide], converted into thioethers [IV; e.g., N-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)thio]-2-hydroxy-2-methylpropanamide] by reaction with mercaptans R2SH (e.g., 4-fluorothiophenol), and then oxidized into their corresponding sulfones.

ST **bicalutamide** prepn

IT Aryl halides
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-arylation of propenamides with)

IT Metal alkoxides
RL: RGT (Reagent); RACT (Reactant or reagent)
(alkali metal, bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Alkali metal compounds
RL: RGT (Reagent); RACT (Reactant or reagent)
(alkoxides, bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Alkali metal hydrides
RL: RGT (Reagent); RACT (Reactant or reagent)
(bases; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Thiols (organic), reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(formation of hydroxy-substituted thioethers from the reaction of epoxides with)

IT Aromatic hydrocarbons, uses
Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(halo, solvents; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Amides, preparation
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(hydroxy; process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Epoxidation
(of N-phenylpropenamides)

IT Epoxides
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(of N-phenylpropenamides in the preparation of intermediates in the preparation of antiandrogenic compds.)

IT Phenylation
(of propenamides in the preparation of intermediates in the preparation of antiandrogenic compds.)

IT Oxidation
(of thioethers into sulfones in the preparation of antiandrogenic compds.)

IT Carboxylic acids, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(peroxy, oxidants; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT Amides, uses
Aromatic hydrocarbons, uses
Esters, uses
Ethers, uses
Hydrocarbons, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvents; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT **109-72-8**, Butyl lithium, reactions 865-47-4 7646-69-7, Sodium hydride 7782-92-5, Sodium amide
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT 79-39-0, Methacrylamide 371-42-6, 4-Fluorothiophenol 407-25-0, Trifluoroacetic anhydride 7722-84-1, Hydrogen peroxide, reactions 194853-86-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT 90356-78-8P 90357-51-0P 90357-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT 359-48-8P, Trifluoroperacetic acid
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(oxidant; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT 79-21-0, Peracetic acid 937-14-4, 3-Chloroperbenzoic acid 7529-22-8, N-Methylmorpholine N-oxide 7790-28-5, Sodium periodate 37222-66-5, Oxone
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidant; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

IT **90357-06-5P, Bicalutamide**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

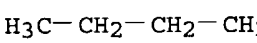
IT **68-12-2**, Dmf, uses **75-09-2**, Dichloromethane, uses **109-99-9**, Thf, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD

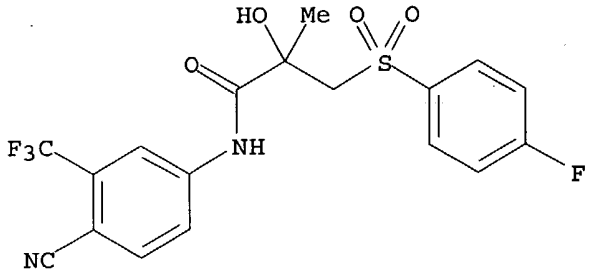
RE

(1) Emmons, W; J AM CHEM SOC 1955, V77(1), P89
(2) Itoh, H; US 4835312 A 1989 HCAPLUS
(3) Tucker, H; US 4636505 A 1987 HCAPLUS
(4) Venier, C; J ORG CHEM 1982, V47(19), P3773 HCAPLUS

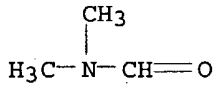
IT **109-72-8**, Butyl lithium, reactions
RL: RGT (Reagent); RACT (Reactant or reagent)
(base; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
RN 109-72-8 HCAPLUS
CN Lithium, butyl- (8CI, 9CI) (CA INDEX NAME)



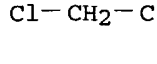
IT **90357-06-5P**, **Bicalutamide**
RL: **SPN (Synthetic preparation)**; **PREP (Preparation)**
(process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




IT **68-12-2**, Dmf, uses **75-09-2**, Dichloromethane, uses **109-99-9**, Thf, uses
RL: NUU (Other use, unclassified); USES (Uses)
(solvent; in a process for the preparation of N-(substituted phenyl)-3-alkyl-, aryl- and heteroarylsulfonyl-2-hydroxy-2-alkyl- and haloalkylpropanamide antiandrogenic compds.)
RN 68-12-2 HCAPLUS
CN Formamide, N,N-dimethyl- (8CI, 9CI) (CA INDEX NAME)



RN 75-09-2 HCAPLUS
CN Methane, dichloro- (8CI, 9CI) (CA INDEX NAME)



RN 109-99-9 HCAPLUS
CN Furan, tetrahydro- (7CI, 8CI, 9CI) (CA INDEX NAME)

L71 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:359958 HCAPLUS
DN 134:366692
ED Entered STN: 18 May 2001
TI Resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs
IN Ekwuribe, Nnochiri N.; James, Kenneth D.
PA Nobex Corporation, USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07C315-06
ICS C07C317-28
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE | |
|---|---|---|---|---|---|---|
| PI | WO 2001034563 | A1 | 20010517 | WO 2000-US41609 | 20001025 | <-- |
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| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| | BR 2000015124 | A | 20020702 | BR 2000-15124 | 20001025 | <-- |
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| | JP 2003513955 | T2 | 20030415 | JP 2001-536512 | 20001025 | <-- |
| | US 6593492 | B1 | 20030715 | US 2000-695884 | 20001025 | <-- |
| | NZ 518552 | A | 20031031 | NZ 2000-518552 | 20001025 | <-- |
| | ZA 2002003228 | A | 20030723 | ZA 2002-3228 | 20020423 | <-- |
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| PRAI | US 1999-161884P | P | 19991027 | <-- | | |
| | WO 2000-US41609 | W | 20001025 | <-- | | |

OS MARPAT 134:366692
AB Title enantiomeric acylanilides were prepared by resolution of R4ZZ1Z2CR1(OH)CO2H [R1 = (halo)alkyl; R4 = (hydroxy)alkyl, alkenyl, (un)substituted Ph, etc.; Z = bond or alkylene; Z1 = O, SO0-2, (alkyl)imino; Z2 = alkylene] followed by amidation.
ST enantiomeric **bicalutamide** analog intermediate resoln
IT 339530-92-6P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)
IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)
IT **339530-91-5**

RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)

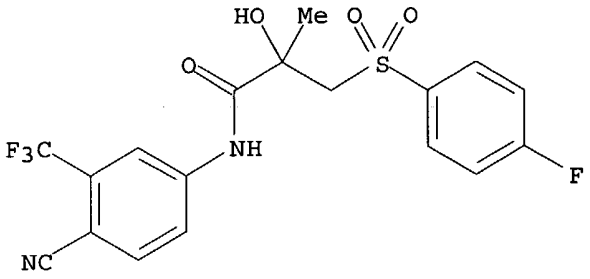
IT 339530-94-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE
(1) Pfizer; WO 9408986 A 1994 HCAPLUS
(2) Sepracor Inc; WO 9519770 A 1995 HCAPLUS
(3) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(4), P885 HCAPLUS

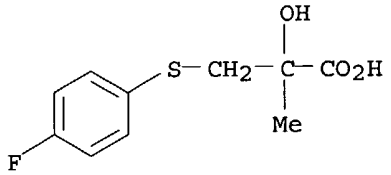
IT **90357-06-5P, Bicalutamide**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)

RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




IT **339530-91-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(resolution of intermediates in the synthesis of enantiomeric **bicalutamide** and analogs)

RN 339530-91-5 HCAPLUS
CN Propanoic acid, 3-[(4-fluorophenyl)thio]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

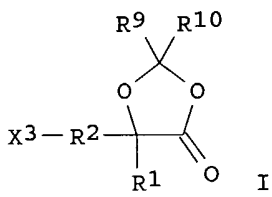



L71 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:300671 HCAPLUS
DN 134:326279
ED Entered STN: 27 Apr 2001
TI Asymmetric synthesis and antiandrogenic use of enantiomers of **Casodex** (**bicalutamide**) and derivatives from enantiomers of citramalic acid or proline.
IN Ekwuribe, Nnochiri
PA Nobex Corporation, USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM C07C315-00
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 2, 63
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2001028990 | A2 | 20010426 | WO 2000-US41233 | 20001018 <-- |
| | WO 2001028990 | A3 | 20010907 | | |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | EP 1222165 | A2 | 20020717 | EP 2000-982690 | 20001018 <-- |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| | BR 2000014889 | A | 20021231 | BR 2000-14889 | 20001018 <-- |
| | JP 2003512351 | T2 | 20030402 | JP 2001-531790 | 20001018 <-- |
| | US 6583306 | B1 | 20030624 | US 2000-691621 | 20001018 <-- |
| | NZ 518392 | A | 20040227 | NZ 2000-518392 | 20001018 <-- |
| | ZA 2002002947 | A | 20030715 | ZA 2002-2947 | 20020415 <-- |
| | NO 2002001831 | A | 20020619 | NO 2002-1831 | 20020418 <-- |
| | US 2004030130 | A1 | 20040212 | US 2003-444343 | 20030523 <-- |
| PRAI | US 1999-160412P | P | 19991019 <-- | | |
| | US 2000-691621 | A3 | 20001018 <-- | | |
| | WO 2000-US41233 | W | 20001018 <-- | | |

OS CASREACT 134:326279; MARPAT 134:326279
GI



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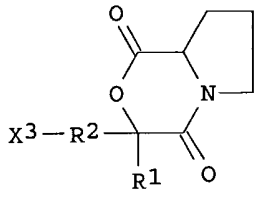

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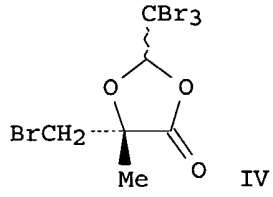
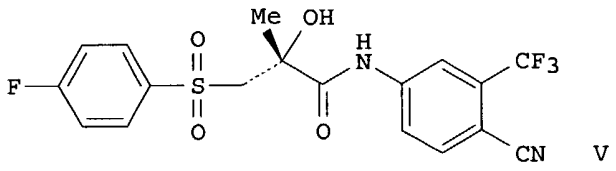


IV



V

AB A method of synthesizing pure enantiomers of acylanilides such as **Casodex** (**bicalutamide**) is disclosed. The method involves contacting certain ring compds. including I, II, or similar gem-disubstituted epoxides with nucleophiles R7-R6-X1H under conditions

sufficient to provide a compound R7-R6-X2-R2-C(OH)(R1)-CO2H [wherein; R1 is alkyl or haloalkyl up to C4; R2 is alkyl up to C6; R6 is a bond or alkyl up to C6; R7 is alk(en)yl, hydroxyalkyl, etc. or R7 is Ph (substituted with up to 3 substituents chosen from H, halo, nitro, carboxy, carbamoyl, etc.); X1 is O, SO0-2, or (alkyl)imino; X2 is O, S(O)0-2 or (oxidized)(alkyl)imino; X3 is a leaving group]. The starting ring compds. are those that, when opened, provide a substituent -R2-C(OH)(R1)-R3 [wherein; R3 is CH2OR4, where R4 is H, PhCH2, C(O)CH3, C(O)OR5, where R5 is H or alkyl]. In an exemplary embodiment, readily available (S)-citramalic acid is reacted with bromal to yield I (R9 = H, R10 is CBr3, R1 is β-Me, R2 is α-CH2 and X3 is CO2H; III). Compound III is condensed with 2-mercaptopyridine-N-oxide using DCC in CBrCl3 (solvent) at reflux which resulted in α-bromination/decarboxylation to IV. Intermediate IV was sequentially treated with base and 4-fluorobenzenethiol, coupled with 4-amino-2-trifluoromethylbenzonitrile and oxidized with mCPBA to give (R)-**Casodex** (V). The order of steps in the conversion of I or II to compds. exemplified by V may vary (e.g. substitution and oxidation of a sidechain of I may precede ring opening). The conversion of (R)-citramalic acid to (S)-**Casodex** is also claimed. Addnl., the invention mentions a modification of a route previously described for the transformation of (R)- and (S)-proline to (R)- and (S)-**Casodex** that improves yield proceeding through a proline-derived intermediate II. Biol. data comparing (R)-, (S)- and (±)-**Casodex**, synthesized by this method, in lowering testosterone response showed (R)-**Casodex** to be substantially more potent than the (S)-isomer.

ST citramalic acid **Casodex bicalutamide** prepn amide nitrile sulfone; prostate cancer **Casodex bicalutamide** amide nitrile sulfone epoxide; asym synthesis **Casodex bicalutamide** nitrile sulfone epoxide; proline **Casodex** conversion improved

IT Androgens
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiandrogens; asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT Antitumor agents
Asymmetric synthesis and induction
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT Prostate gland
(neoplasm, treatment of with enantiomeric **Casodex**; asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT **90357-06-5, Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT **113299-38-0P, S-Casodex 113299-40-4P, R-Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **IMF (Industrial manufacture); SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

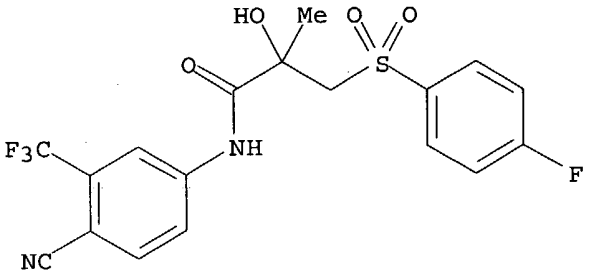
IT 90357-17-8P 335595-47-6P 335595-50-1P 335595-52-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT 115-17-3, Bromal 371-42-6, 4-Fluorobenzenethiol 597-44-4, Citramalic acid **654-70-6**, 4-Amino-2-trifluoromethylbenzonitrile 1121-31-9, 2-Mercaptopyridine N-oxide 6236-09-5, S-Citramalic acid 6236-10-8, R-Citramalic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

IT **90357-06-5, Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

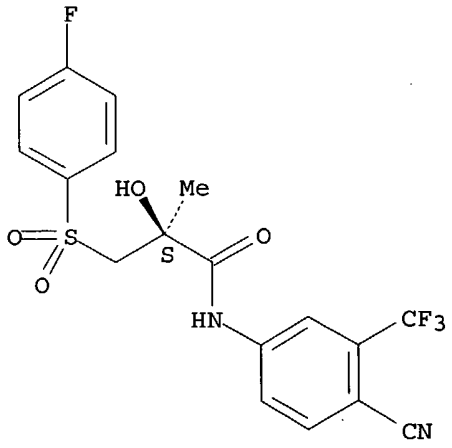
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)




IT **113299-38-0P**, S-**Casodex** **113299-40-4P**, R-**Casodex**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); **IMF (Industrial manufacture)**; **SPN (Synthetic preparation)**; THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)

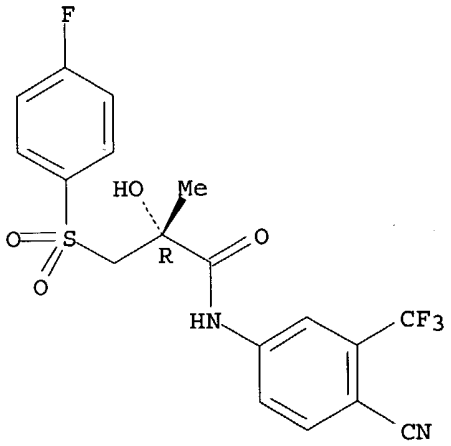
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

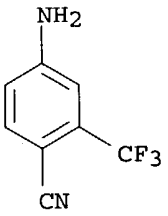


RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **654-70-6**, 4-Amino-2-trifluoromethylbenzonitrile
RL: RCT (Reactant); RACT (Reactant or reagent)
(asym. synthesis (and use) of (R)- and (S)-**Casodex** (**bicalutamide**) from (S)- and (R)-citramalic acid)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L71 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:12441 HCAPLUS
DN 134:86040
ED Entered STN: 05 Jan 2001
TI Preparation of **bicalutamide** enantiomers
IN Soros, Bela; Tuba, Zoltan; Galik, Gyorgy; Bor, Adam; Demeter, Adam; Trischler, Ferenc; Horvath, Janos; Brlik, Janos
PA Richter Gedeon Vegyeszeti Gyar Rt., Hung.
SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D327-10
ICS C07C253-30; C07C303-28; C07C309-66; C07C319-14; C07C323-60; C07C315-02; C07C317-46
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2001000608 | A1 | 20010104 | WO 2000-HU49 | 20000526 <-- |

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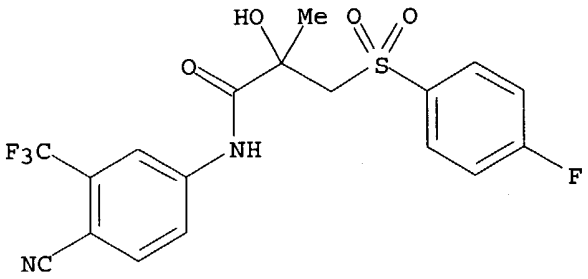
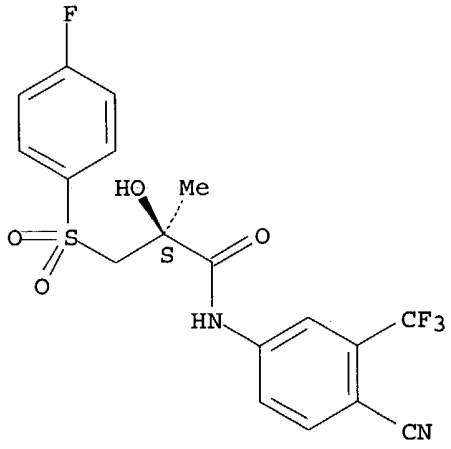
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1189898 A1 20020327 EP 2000-937111 20000526 <--
EP 1189898 B1 20030312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
AT 234294 E 20030315 AT 2000-937111 20000526 <--
ES 2188550 T3 20030701 ES 2000-937111 20000526 <--
PRAI HU 1999-1937 A 19990610 <--
WO 2000-HU49 W 20000526 <--
OS CASREACT 134:86040
AB Racemic HOCH2CMe(OH)CO2H was optically resolved and the enantiomers treated with SOCL2 to give the dioxothiolanonecarbonyl chloride which was amidated by H2NC6H3(CF3)(CN)-3,4. The deprotected dihydroxyamide was O-acylated by RSO2Cl (R = 4-Me- or -BrC6H4) and the product thioetherified by 4-FC6H4SNa to give, after oxidation, the title compds.
ST **bicalutamide** enantiomer prepn
IT 316373-87-2P 316373-88-3P
RL: IMF (Industrial manufacture); PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **bicalutamide** enantiomers)
IT 90356-78-8P 90357-17-8P 90357-18-9P 149404-64-8P 316373-86-1P 316373-89-4P 316373-90-7P 316373-91-8P 316373-92-9P 316373-93-0P 316373-94-1P 316373-95-2P 316373-96-3P 316373-97-4P 316373-98-5P 316373-99-6P 316374-00-2P 316374-01-3P 316374-02-4P 316374-03-5P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **bicalutamide** enantiomers)
IT **90357-06-5P 113299-38-0P 113299-40-4P**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of **bicalutamide** enantiomers)
IT 98-58-8, p-Bromobenzenesulfonyl chloride 98-59-9, p-Toluenesulfonyl chloride 371-42-6, 4-Fluorothiophenol **654-70-6**, 4-Cyano-3-trifluoromethylaniline 21620-60-0, 2,3-Dihydroxy-2-methylpropionic acid 99306-87-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **bicalutamide** enantiomers)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Imperial Chemical Industries; EP 0100172 A 1984 HCAPLUS
(2) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(4), P885 HCAPLUS
(3) Tucker, H; JOURNAL OF MEDICINAL CHEMISTRY 1988, V31(5), P954 HCAPLUS
IT **90357-06-5P 113299-38-0P 113299-40-4P**
RL: **IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)**
(preparation of **bicalutamide** enantiomers)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



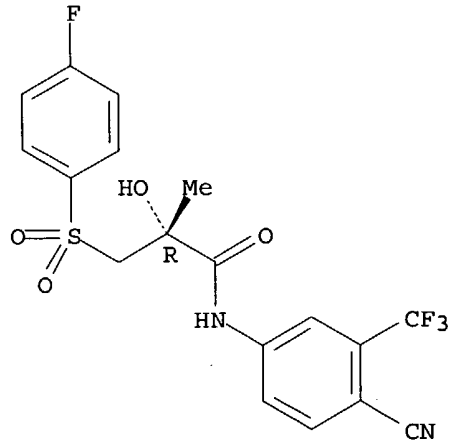
RN 113299-38-0 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



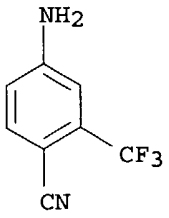
RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

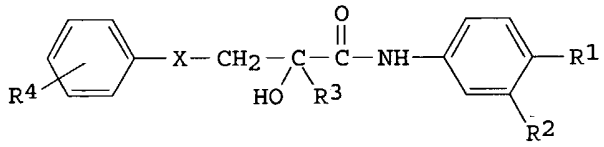


IT **654-70-6**, 4-Cyano-3-trifluoromethylaniline
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of **bicalutamide** enantiomers)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L71 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:161557 HCAPLUS
DN 108:161557
ED Entered STN: 13 May 1988
TI Nonsteroidal antiandrogens. Synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides
AU Tucker, Howard; Crook, J. W.; Chesterson, G. J.
CS Pharm. Div., Imp. Chem. Ind. PLC, Macclesfield/Cheshire, AK10 4TG, UK
SO Journal of Medicinal Chemistry (**1988**), 31(5), 954-9
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
CC 2-2 (Mammalian Hormones)
Section cross-reference(s): 1
OS CASREACT 108:161557
GI



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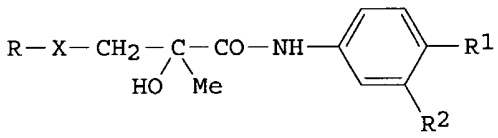

II

AB A series of hydroxypropionanilides of general structure I and II (R1,R2 = NO2, CF3, CN, or Cl; R3 = CF3 or CH3; R4 = H, Cl, F, NO2, CN, MeO, or MeS; X = S, SO, or SO2; and R = alkyl or heterocyclic derivs.) were prepared and tested for antiandrogen activity by their effects on accessory sex organs in rats. A series of compds. where R3 = CF3 generally exhibited partial androgen agonist activity, whereas those compds. where R3 = CH3 were pure antagonists. Optimization of the latter series of compds. led to novel, potent antiandrogens which were peripherally selective.
ST nonsteroidal antiandrogen structure activity; hydroxypropionanilide antiandrogen structure activity
IT Androgens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor, thiohydroxypropionanilide derivs. as)
IT Molecular structure-biological activity relationship
(androgen-inhibiting, of thiohydroxypropionanilide derivs.)

IT 95-76-1 100-01-6, reactions 393-11-3 635-22-3 **654-70-6**
825-41-2 20925-27-3 72115-06-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling of, with α-hydroxy acid chloride in dimethylacetamide)
IT 90357-42-9P 112988-42-8P 112988-43-9P 112988-44-0P 112988-45-1P
112988-46-2P 112988-47-3P 112988-48-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acid hydrolysis of)
IT 5042-53-5P 14109-72-9P 17078-37-4P 20996-62-7P 25784-83-2P
34509-09-6P 92682-40-1P 112988-41-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and addition reaction of, with cyanide)
IT 112988-50-8DP, derivs.
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antiandrogen activity of)
IT 90356-00-6P 90356-01-7P 90356-03-9P 90356-06-2P 90356-09-5P
90356-10-8P 90356-13-1P 90356-15-3P 90356-16-4P 90356-20-0P
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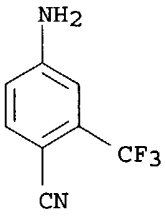
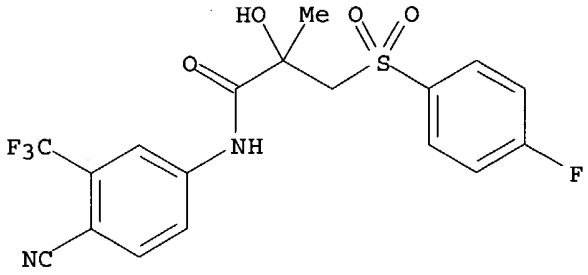
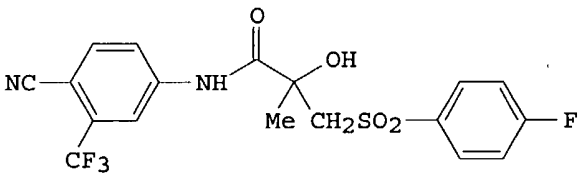
90357-05-4P **90357-06-5P** 90357-07-6P 90357-09-8P
90357-19-0P 112988-36-0P 112988-37-1P 112988-38-2P 112988-39-3P
112988-40-6P
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and antiandrogen activity of, structure in relation to)
IT 90357-22-5P 90357-26-9P 90357-27-0P 90357-28-1P 90357-29-2P
90357-34-9P 90357-35-0P 112988-49-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and coupling of, with aniline in dimethylacetamide)
IT 90357-52-1P 90357-53-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and epoxidn. of)
IT 90357-50-9P 90357-51-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with thiols)
IT 74-93-1, reactions 75-08-1 75-33-2 106-54-7 107-03-9 108-98-5, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with bromoacetone and bromotrifluoroacetone)
IT 75-66-1 110-66-7 149-30-4 371-42-6 696-63-9 1122-97-0
1450-85-7 1849-36-1 2037-31-2 2637-34-5 4556-23-4 5685-05-2
5685-06-3 6320-03-2 7774-74-5 16133-26-9 29490-19-5 36801-01-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with epoxides)
IT 431-35-6, Bromotrifluoroacetone 598-31-2, Bromoacetone
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with thiols)
IT **654-70-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling of, with α-hydroxy acid chloride in dimethylacetamide)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



IT **90357-06-5P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and antiandrogen activity of, structure in relation to)
RN 90357-06-5 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)



L71 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1988:150026 HCAPLUS
DN 108:150026
ED Entered STN: 30 Apr 1988
TI Resolution of the non-steroidal antiandrogen 4'-cyano-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide and the determination of the absolute configuration of the active enantiomer
AU Tucker, Howard; Chesterson, Glynne J.
CS Pharm. Div., Imp. Chem. Ind. PLC, Mereside/Macclesfield/Cheshire, SK10 4TG, UK
SO Journal of Medicinal Chemistry (**1988**), 31(4), 885-7
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
CC 25-20 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1
OS CASREACT 108:150026
GI



I

AB The nonsteroidal antiandrogen 4'-cyano-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-3'-(trifluoromethyl)propionanilide (I) has been resolved by chromatog. separation of the diastereomeric (R)-camphanyl esters of the precursor thioether followed by hydrolysis and oxidation of the isolated enantiomers. In addition, an asym. synthesis of (S)-3-bromo-2-hydroxy-2-methylpropanoic acid and subsequent conversion into the (S)-sulfone has established that the more potent enantiomer of I has the R absolute configuration.

ST cyanotrifluoromethylpropionanilide fluorophenylsulfonyl resoln antiandrogen

IT Androgens
RL: USES (Uses)
(inhibitors, cyanotrifluoromethyl(fluorophenylsulfonyl)propionanilide derivative)

IT Resolution
(of cyanotrifluoromethyl(fluorophenylsulfonyl)chloropropionyl derivative)

IT 51161-88-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(bromination of)

IT 371-42-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyanoetherification of)

IT 90357-17-8P **113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and antiandrogen activity of)

IT 113181-02-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and cyanoetherification of)

IT 106089-19-4P 113181-03-6P 113299-39-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 106089-20-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, chlorination, and amidation of)

IT 90357-18-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation, oxidation, and antiandrogen activity of)

IT 90356-78-8
RL: PROC (Process)
(resolution of)

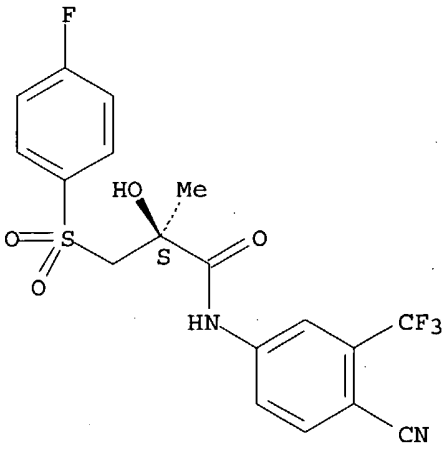
IT **654-70-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation of)

IT **113299-38-0P 113299-40-4P**
RL: **SPN (Synthetic preparation); PREP (Preparation)**
(preparation and antiandrogen activity of)

RN 113299-38-0 HCAPLUS

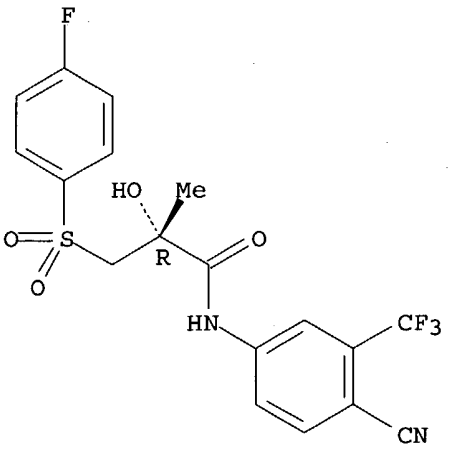
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

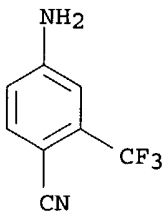


RN 113299-40-4 HCAPLUS
CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **654-70-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(N-acylation of)
RN 654-70-6 HCAPLUS
CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



L71 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1984:454739 HCAPLUS

DN 101:54739
ED Entered STN: 18 Aug 1984
TI Amide derivatives
IN Tucker, Howard
PA Imperial Chemical Industries PLC, UK
SO Eur. Pat. Appl., 53 pp.
CODEN: EPXXDW
DT Patent
LA English
IC C07C149-23; C07C149-41; C07C103-375; C07C103-50; C07C121-78; C07C147-107; C07C147-14; C07D213-70; C07D247-02; C07D283-02; C07D285-12
CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1
FAN.CNT 1

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| PI | EP 100172 | A1 | 19840208 | | EP 1983-303998 | 19830708 | <-- |
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| | AU 556328 | B2 | 19861030 | | | | |
| | HU 32058 | O | 19840628 | | HU 1983-2531 | 19830718 | <-- |
| | HU 191296 | B | 19870227 | | | | |
| | FI 8302644 | A | 19840124 | | FI 1983-2644 | 19830720 | <-- |
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| | JP 59033250 | A2 | 19840223 | | JP 1983-131085 | 19830720 | <-- |
| | JP 04032061 | B4 | 19920528 | | | | |
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| | ES 539614 | A1 | 19860601 | | ES 1985-539614 | 19850116 | <-- |
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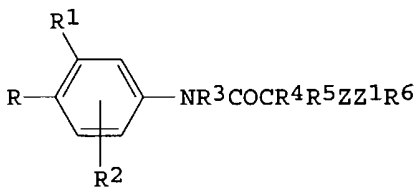


I

AB Antiandrogenic (no data) alkananilides including I [R = alkanoyl, halo, cyano, NO2, alkylthio, alkylsulfinyl, alkylsulfonyl, PhS, PhSO, PhSO2, etc.; R1 = H, alkyl, alkoxy, R; R2 = H, halo; R3 = H, alkyl; R4 = H, OH, alkoxy, acyloxy; R5 = alkyl, haloalkyl; R4R5 = CO2; R6 = (un)substituted alkyl, alkenyl, Ph, naphthyl, heterocyclyl; Z = bond, alkylene; Z1 = O, S,

S(O), SO2, NR7; R7 = H, alkyl] (124 compds.) were prepared Thus, Me 2,3-epoxy-2-methylpropionate, prepared by epoxidn. of H2C:CMeCO2Me, was treated with NaH and PhSH to give PhSCH2CMe(OH)CO2Me. This was saponified to give the free acid which was treated with SOCl2 and 4,3-(NC)(F3C)C6H3NH2 to give 4,3-(NC)(F3C)C6H3NHCOCMe(OH)CH2SPh.

ST antiandrogenic phenylthiohydroxypropionanilide; propionanilide hydroxy phenylthio; aniline alkanoylation; glycidate alkanethiol benzenethiol

IT Androgens
RL: USES (Uses)
(inhibitors, hydroxypropionanilides)

IT 80-59-1 565-63-9 920-46-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation by, of anilines)

IT 95-76-1 393-11-3 635-22-3 **654-70-6** 825-41-2 7251-09-4 20925-27-3 56765-79-8 72115-06-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of, by glycidates and hydroxypropionates)

IT 431-35-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of thiols)

IT 87310-62-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with Me Ph sulfide and (methylsulfonyl)thiophene)

IT 74-93-1, reactions 75-33-2 100-53-8 107-03-9 1849-36-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with bromotrifluoroacetone)

IT 60-24-2 60-56-0 75-08-1 96-53-7 106-54-7 108-98-5, reactions 110-66-7 149-30-4 371-42-6 696-63-9 870-23-5 1122-97-0 1450-85-7 1679-07-8 2037-31-2 2637-34-5 4556-23-4 5685-05-2 5685-06-3 5954-68-7 6320-03-2 7774-74-5 16133-26-9 29490-19-5 36801-01-1 40771-41-3 67131-59-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with glycidates)

IT 100-68-5 90357-57-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation of, with pyruvanilide)

IT 58653-97-7P 65925-77-1P 90357-50-9P 90357-51-0P 90357-56-5P 90366-53-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and condensation of, with thiols)

IT 90357-14-5P 90410-51-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and decomposition of)

IT 2164-09-2P 90357-52-1P 90357-53-2P 90357-54-3P 90357-55-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and epoxidn. of)

IT 34509-09-6P 90357-44-1P 90357-45-2P 90357-46-3P 90357-47-4P 90357-48-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrocyanation of)

IT 90357-42-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)

IT 90356-00-6P 90356-01-7P 90356-04-0P 90356-05-1P 90356-07-3P 90356-08-4P 90356-14-2P 90356-17-5P 90356-18-6P 90356-19-7P 90356-38-0P 90356-60-8P 90356-70-0P 90356-78-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and oxidation of)

IT 64454-43-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and saponification of)

IT 90356-02-8P 90356-03-9P 90356-06-2P 90356-09-5P 90356-10-8P
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90357-19-0P 90357-20-3P 90357-21-4P 90357-43-0P 90373-25-4P

RL: **SPN (Synthetic preparation); PREP (Preparation)**

(preparation of)

IT 90357-22-5P 90357-25-8P 90357-26-9P 90357-27-0P 90357-28-1P
90357-29-2P 90357-30-5P 90357-31-6P 90357-32-7P 90357-33-8P
90357-34-9P 90357-35-0P 90357-36-1P 90357-37-2P 90357-38-3P
90357-39-4P 90357-40-7P 90357-41-8P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, and acylation of anilines by)

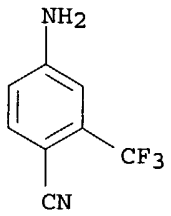
IT **654-70-6**

RL: RCT (Reactant); RACT (Reactant or reagent)

(acylation of, by glycidates and hydroxypropionates)

RN 654-70-6 HCAPLUS

CN Benzonitrile, 4-amino-2-(trifluoromethyl)- (9CI) (CA INDEX NAME)



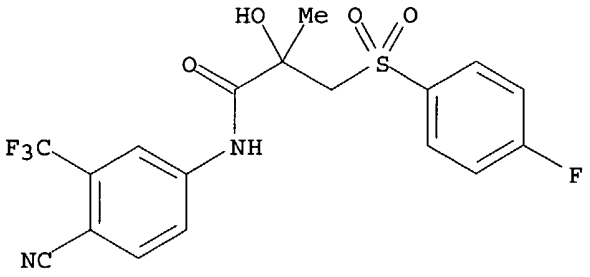

IT **90357-06-5P**

RL: **SPN (Synthetic preparation); PREP (Preparation)**

(preparation of)

RN 90357-06-5 HCAPLUS

CN Propanamide, N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl- (9CI) (CA INDEX NAME)

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    NEW FORMAT GERMAN PATENT APPLICATION AND PUBLICATION
    NUMBERS. SEE ALSO:
    http://www.stn-international.de/archive/stnews/news0104.pdf <<<

>>> SINCE THE FILE HAD NOT BEEN UPDATED BETWEEN APRIL 12-16
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DC   A96 B05
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PA   (WEST-I) WESTHEIM R J H; (SYNT-N) SYNTHON BV
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WO 2004029021 A1 20040408 (200431) EN C07C317-46
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
ADT US 2004063782 A1 Provisional US 2002-413765P 20020927, Provisional US 2003-470223P 20030514, US 2003-660775 20030912; WO 2004029021 A1 WO 2003-EP10933 20030925
PRAI US 2003-660775 20030912; US 2002-413765P 20020927;
US 2003-470223P 20030514
IC ICM A61K031-277; C07C317-46
AB US2004063782 A UPAB: 20040514
NOVELTY - Polymorphic forms including **crystalline** form (II) (A1) and amorphous form (B1) of **bicalutamide** are new.
DETAILED DESCRIPTION - Polymorphic forms including **crystalline** form (II) (A1) and amorphous form (B1) of **bicalutamide** are new.
INDEPENDENT CLAIMS are included for following
(1) a composition (C1) comprising (A1), at least one of **crystalline bicalutamide** of form (I), and (B1);
(2) a composition (C2) comprising (A1), and an excipient; and
(3) preparation of the polymorphic forms.
ACTIVITY - Cytostatic.
MECHANISM OF ACTION - Androgenic inhibitor.
USE - For treating prostate cancer and having anti-androgenic activity.
ADVANTAGE - The **bicalutamide** of form (II) is isolated in a relatively pure form with at least 98% purity. The polymorphic forms exhibit better stability than the prior art excellent antiandrogenic activity and hence are effective for treating prostate cancer.
Dwg.0/8
FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C02A1; B04-C02A2; B04-C02B2; B07-A02B; B10-A10; B14-D02A; B14-H01; B14-N07A
TECH UPTX: 20040514
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (A1) involves:
(a) Process A: precipitating (A1) from a solution containing **bicalutamide** in the presence of seed **crystals** of form (II) by lowering the temperature of the solution and/or contacting with a contrasolvent at least 35 degrees C; and
(b) Process B: heating (B1) to get **crystals** of (A1).
Preparation of (B1) involves heating a solid form of **bicalutamide** to form a melt and cooling the resultant melt.
Preferred Components: Form (II) is characterized by an X-ray diffraction pattern as given in the specification. The **crystalline** form is racemic. The excipient is a carrier or diluent (preferably **microcrystalline** cellulose, hydroxypropyl methylcellulose, lactose or starch).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The excipient is calcium phosphate.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: (C2) Comprises form (II) (0.1 - 99.9 wt.%). (C2) Is substantially free of the form (I), but optionally comprises the form (I). (C2) Is in an unit dose formulated as solid oral dosage form, solution or suspension.

ABEX UPTX: 20040514
ADMINISTRATION - Administration of (A1) is orally (claimed). Dosage is 0.1 - 125 mg/kg or 1 - 600 (preferably 1 - 300, especially 50 - 150) mg.
EXAMPLE - **Bicalutamide** form (I) (1 g) was heated in an oil bath at 210 degrees C for 5 minutes. The resultant melt was cooled to room temperature; and again heated in the oil bath at 160 degrees C. Within few minutes **crystals** of **bicalutamide** form (II) were formed. The resultant **crystals** (5 mg) were suspended in n-heptane (7 ml) and the suspension was stirred with a magnetic stirrer in a water bath. **Bicalutamide** form (I) (0.5 g) was dissolved in ethyl acetate (7 ml) at reflux. The warm solution was added dropwise to the stirred cold heptane suspension. The resultant milky suspension was filtered under reduced pressure, and dried at ambient temperature under vaccum for 1.5 hours. **Bicalutamide** (190 g) was dissolved in ethyl acetate (2.52 ml) at reflux, and was added to n-heptane (3 ml) which was cooled to -5 to -10 degrees C and seeded with the form (I) (200 mg). The resultant suspension was stirred for 5 minutes, filtered, washed with cold n-heptane, and dried to get **crystalline** **bicalutamide** form (II) (160 g, 99.78% purity).

L92 ANSWER 2 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-248621 [24] WPIX
DNC C2004-097261
TI **Casodex** synthesizing process for anti-tumour medicine.
DC B05
IN LU, W; XIA, Y; ZHU, Q
PA (SHAN-N) SHANGHAI MEDICINE INST CHINESE ACAD SCI
CYC 1
PI CN 1458146 A 20031126 (200424)* C07C317-32
ADT CN 1458146 A CN 2002-111681 20020515
PRAI CN 2002-111681 20020515
IC ICM C07C317-32
ICS A61P035-00; **C07C315-02**
AB CN 1458146 A UPAB: 20040408
NOVELTY - The present invention provides the new synthesis process of **Casodex** as a kind of antitumor medicine. During the syntheis of **Casodex**, it is needed to oxidize thioether intermediate into sulfone, and available industrial oxidation process adopts acid peroxide as oxidant, which is expensive, explosive and pollutant. The present invention uses hydrogen peroxide as oxidant and produces the product through reaction in proper solvent, in the presence of catalyst and at certain temperature. The present invention has high product yield and purity, no any environmental pollution, simple operation and treatment, and is suitable for industrial production.
Dwg.0/0
FS CPI
FA AB
MC CPI: B10-B04A; B10-H02; B14-H01

L92 ANSWER 3 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-118871 [12] WPIX
CR 2004-315002 [29]
DNC C2004-047589
TI Preparation of **bicalutamide**, useful for treating prostate cancer and other androgen dependent conditions, comprises reacting 4-fluorobenzene sulfinic acid salt with reaction partner.
DC B05
IN ETTEMA, G J B; KELTJENS, R; THIJS, L
PA (SYNT-N) SYNTHON BV
CYC 105
PI US 2003073742 A1 20030417 (200412)* 24 A61K031-277
WO 2004031136 A1 20040415 (200426) EN C07C315-00 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS

LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

ADT US 2003073742 A1 US 2002-261492 20021002; WO 2004031136 A1 WO 2003-EP11166 20031001

PRAI US 2002-261492 20021002

IC ICM A61K031-277; **C07C315-00**
ICS **C07C315-04**; C07C317-32; C07C317-46

AB US2003073742 A UPAB: 20040505
NOVELTY - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).

DETAILED DESCRIPTION - Preparation of **bicalutamide** (I) comprises reacting a 4-fluorobenzene sulfinic acid salt of formula (II) with a reaction partner to form (I) and a non **bicalutamide** product (II) and converting (II) to (I).

Z = a cation.

An INDEPENDENT CLAIM is also included for new compounds of formula (IV).

A = OR;

X = H, or

A + X = 5-10 membered optionally fused heterocyclyl, and

R = 1-6C alkyl, 3-6C cycloalkyl, phenyl or benzyl,

provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.

ACTIVITY - Cytostatic.

No biological data available.

MECHANISM OF ACTION - Androgen inhibitor.

USE - Used as a non-steroidal antiandrogen agent used in the treatment of prostate cancer and other androgen dependent conditions.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A10; B14-D02; B14-H01; B14-L06

TECH UPTX: 20040218
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: The reaction partner comprises Y-CH2-C(Me)(OX1)-COA1, L-CH2-C(Me)=CH2 or L-CH2-COMe.

A1 = OR or 3-trifluoromethyl-4-cyanophenylamino;

Y = a leaving group;

X1 = H, or

X1 + Y = 3-6 membered heterocyclyl, or

X1 + A1 = 5- or 6-membered heterocyclyl, and

L = halo.

(II) Is reacted with Y1-CH2-C(Me)(OX2)-COA2 to form a compound of formula (IVA).

Y1 = a leaving group;

A2 = OR or 3-trifluoromethyl-4-cyanophenylamino, and

X2 = H, or

X2 + Y1 = 3-6 membered heterocyclyl, or

X2 + A2 = 5-10 membered optionally fused heterocyclyl,

Provided that if a ring N atom is present, it is optionally substituted by 3-trifluoromethyl-4-cyanophenyl.

Reaction of (II) with a reaction partner is effected in a biphasic reaction system or in a lower alcohol. A2 is 3-trifluoromethyl-4-cyanophenylamino and (IVA) is (I). Y1-CH2-C(Me)(OX2)-COA2 is optically active and (I) is enriched R-(I). (I) Is racemic and R-(I) isomer is isolated.

ABEX UPTX: 20040218
EXAMPLE - In a flask (25 ml) with a magnetic stirrer, N-(4-cyano-3-

(trifluoromethyl)phenyl)-2-hydroxy-3-iodo-2-methylpropanamide (0.200 g) and sodium p-fluorobenzenesulfinate (0.2 g) were dissolved in dimethylsulfoxide (3-4 ml) and heated at 60 degrees C for 18 hours. During the reaction, the next three portions of sodium p-fluorobenzenesulfinate (0.200 g) were added. The reaction was followed by high performance liquid chromatography analysis. To the reaction mixture was added ethyl acetate (30 ml), brine (30 ml) and water (20 ml). The organic layer was washed with 0.5N aqueous HCl (20 ml), water (20 ml) and saturated aqueous NaHCO3 (20 ml). After drying (Na2SO4) and concentration in vacuo, the crude product was purified by column chromatography (Merck60 SiO2; eluent = ethyl acetate/heptane = 3/2) to give **bicalutamide** (0.050 g; 23%).

DEFINITIONS - Preferred Definitions:
Z = alkali metal, Mg halide or ammonium.

L92 ANSWER 4 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-012518 [01] WPIX
DNC C2004-003809
TI Pure **bicalutamide** preparation, useful as antiandrogen in treating prostate cancer, from epoxide or halohydrin (or their precursors) and p-fluorophenylsulfinate salt.
DC B05
IN BOR, A; LUKACS, F; OROSZ, G; SCHNEIDER, G
PA (CFPH-N) CF PHARMA GYOGYSZERGYARTO KFT; (HELM-N) HELM AG
CYC 103
PI WO 2003097590 A1 20031127 (200401)* GE 26 C07C315-00 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
DE 10222104 A1 20031204 (200401) C07C315-00 <--
ADT WO 2003097590 A1 WO 2003-EP4999 20030513; DE 10222104 A1 DE 2002-10222104 20020517
PRAI DE 2002-10222104 20020517
IC ICM **C07C315-00**
ICS C07C317-46
AB WO2003097590 A UPAB: 20040102
NOVELTY - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide (I) involves reacting N-(4-cyano-3-trifluoromethyl-2-methyl-oxirane-2-carboxamide or a corresponding halohydrin (or their precursors) with a p-fluorophenylsulfinate salt (IV) and if necessary converting the precursor residue.

DETAILED DESCRIPTION - Preparation of N-(4-cyano-3-trifluoromethyl-phenyl)-3-(4-fluorophenylsulfonyl)-2-hydroxy-2-methyl-propionamide of formula (I) involves reacting an epoxide of formula (II) or a halohydrin (or analog) of formula (III) with a p-fluorophenylsulfinate salt (IV) and if necessary converting a precursor group R into N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl.

R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or its precursor;

X = leaving group.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - (I) is an antiandrogen useful in the treatment of prostate carcinoma.

ADVANTAGE - Racemic or enantiomeric (I) is obtained in pharmaceutically acceptable purity by a simple and economical procedure, using (IV) as starting material (rather than the highly toxic

p-fluorothiophenol plus expensive and/or dangerous oxidizing agents as in prior art methods).
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B10-A10; B14-D02A; B14-H01
TECH UPTX: 20040102
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (II) is obtained from (III), conversion of (III) to (II) and reaction of (II) with (IV) preferably being carried out as a one-pot reaction. (II) or (III) is racemic or optically active R- or S-enantiomer form. (IV) is an alkali metal p-fluorophenylsulfinate, preferably the sodium salt.
ABEX UPTX: 20040102
SPECIFIC COMPOUNDS - (I) is specifically disclosed as **bicalutamide**
.

EXAMPLE - A mixture of 7.0 g N-(4-cyano-3-trifluoromethyl-phenyl)-2-methyl-oxirane-2-carboxamide, 9.43 g sodium p-fluorophenylsulfinate, 50 ml methanol and 3 ml glacial acetic acid was heated under reflux for 5 hours, then evaporated. The residue was partitioned between dichloromethane and water, and the organic phase was washed, dried and evaporated. The residue was **recrystallized** from diisopropyl ether to give 7.1 g of **bicalutamide**, m.pt. 187-189 degrees C, purity 96.6% (by HPLC).

DEFINITIONS - Preferred Definitions:
R = N-(4-cyano-3-trifluoromethyl-phenyl)-aminocarbonyl or -CO-Y;
X = halo (e.g. Cl, Br or I) or alkyl- or arylsulfonate (e.g. mesylate, tosylate or brosylate).

L92 ANSWER 5 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-607903 [57] WPIX
DNC C2003-165631
TI Preparation of **bicalutamide** from N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline and monohypophthalic acid.
DC B05
IN ITAYA, N; KATSURA, T; SHINTAKU, T
PA (ITAY-I) ITAYA N; (KATS-I) KATSURA T; (SHIN-I) SHINTAKU T; (SUMO) SUMIKA FINE CHEM CO LTD
CYC 101
PI WO 2003053920 A1 20030703 (200357)* JA 46 C07C315-02 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2003191337 A1 20031009 (200367) C07C317-34
C07C315-02 <--
AU 2002354475 A1 20030709 (200428) C07C315-02 <--
ADT WO 2003053920 A1 WO 2002-JP13058 20021213; US 2003191337 A1 WO 2002-JP13058 20021213, US 2003-362410 20030224; AU 2002354475 A1 AU 2002-354475 20021213
FDT AU 2002354475 A1 Based on WO 2003053920
PRAI JP 2002-166213 20020606; JP 2001-380686 20011213
IC ICM **C07C315-02**; C07C317-34
ICS A61K031-277; A61K031-2777; A61P005-28; A61P005-288; A61P043-00; A61P043-000; **C07C315-06**; **C07C315-066**; C07C317-46; C07C317-466
AB WO2003053920 A UPAB: 20030906
NOVELTY - Preparation of **bicalutamide** (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III).

DETAILED DESCRIPTION - Preparation of **bicalutamide** of formula (I) includes the step of reacting N-methacroyl-4-cyano-2-methylpropionyl-3-trifluoromethaneaniline of formula (II) with monoperphthalic acid to give 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline of formula (III).

INDEPENDENT CLAIMS are also included for:

(1) preparation of (I) which includes the step of reacting 4'-cyano-3-(4-fluorophenylthio)-2-hydroxy-2-methyl-3'-trifluoromethylpropionanilide of formula (IV) either with monoperphthalic acid or with hydrogen peroxide in the presence of a sodium tungstenate or its solvate, phenylsulfonic acid or a phase transfer catalyst in ethyl acetate;

(2) preparation of **crystalline** (I) comprising dissolving (I) in ethyl acetate, adding hexane, heptane or a similar hydrocarbon solvent, and **crystallizing** (I) from the solvent mixture; and

(3) **crystalline** (I) having 13C-NMR data given in the specification.

USE - For preparing **bicalutamide** preferably in **crystalline** form useful as an antiandrogenic agent.

ADVANTAGE - Processes are environmentally friendly, economical, efficient and safe.

Dwg.0/1

FS CPI
FA AB; GI; DCN
MC CPI: B05-A01B; B05-A03B; B07-A03; B10-A10; B10-A15; B14-D02
TECH UPTX: 20030906

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process: (IV) Is oxidized is using 3-6 moles hydrogen peroxide per mole of (IV) in the presence of 0.5-5 moles of catalyst.

ABEX UPTX: 20030906

EXAMPLE - Monoperphthalic acid (108.05 g, then 19.82 g) was added to N-methacroyl-4-cyano-2-methylpropionyl)-3-trifluoromethaneaniline (II) (13.8 g) in ethyl acetate at 50-55 degrees C and the mixture was stirred at 50-55 degrees C for 3.9 hours. Monoperphthalic acid (10.36 g, then 1.90 g) was added and the mixture was reacted for a further hour. Work-up gave 4-cyano-N-(2,3-epoxy-2-methylpropionyl)-3-trifluoromethylaniline (III) (11.37 g; 77.3 % yield; 98.7 % purity).

L92 ANSWER 6 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-156908 [15] WPIX
DNC C2003-040799
TI Preparation of rac-**bicalutamide** useful for selectively reducing testosterone level, comprising addition of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionic acid to 5-amino-2-cyano-benzotrifluoride and butyl lithium in organic solvent.
DC B05
IN **DOLITZKY, B**; **REANY, O**; **SHAMMAI, J**; **SHAMAI, J**
PA (BIOG) **BIOGAL GYOGYSZERGYAR**; (DOLI-I) DOLITZKY B; (REAN-I) REANY O; (SHAM-I) SHAMMAI J; (BIOG) **BIOGAL GYOGYSZERGYAR RT**; (TEVA-N) **TEVA PHARM IND LTD**; (TEVA-N) **TEVA PHARM USA INC**
CYC 101
PI WO 2002100339 A2 20021219 (200315)* EN 11 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003045741 A1 20030306 (200320) C07C315-04 <--
US 2004044249 A1 20040304 (200417) C07C317-28 <--
US 2004059147 A1 20040325 (200422) C07C317-24

EP 1406855 A2 20040414 (200426) EN C07C069-675
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 6737550 B2 20040518 (200433) C07C315-04 <--

ADT WO 2002100339 A2 **WO 2002-US18329 20020613**; US 2003045741 A1 **Provisional US 2001-298009P 20010613, Provisional US 2002-371069P 20020409**, US 2002-170721 20020613; US 2004044249 A1 **Provisional US 2001-298009P 20010613, Provisional US 2002-371069P 20020409**, CIP of US 2002-170721 20020613, US 2003-606403 20030625; US 2004059147 A1 **Provisional US 2001-298009P 20010613, Provisional US 2002-371069P 20020409**, Div ex US 2002-170721 20020613, US 2003-668982 20030922; EP 1406855 A2 EP 2002-739801 20020613, **WO 2002-US18329 20020613**; US 6737550 B2 **Provisional US 2001-298009P 20010613, Provisional US 2002-371069P 20020409**, US 2002-170721 20020613

FDT EP 1406855 A2 Based on WO 2002100339

PRAI **US 2002-371069P 20020409; US 2001-298009P 20010613**; US 2002-170721 20020613; US 2003-606403 20030625; US 2003-668982 20030922

IC ICM A61K000-00; C07C069-675; **C07C315-04**; C07C317-24; C07C317-28
ICS C07C255-49; C07C255-50; C07C317-14

AB WO2002100339 A UPAB: 20030303
NOVELTY - Preparation (P1) of rac-**bicalutamide** (I) (both R- and S- isomers) comprises addition of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionic acid (i) to a mixture of 5-amino-2-cyano-benzotrifluoride and butyl lithium in an organic solvent, and recovering.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a rac-**bicalutamide** intermediate of formula (X) or (Y), which represent stable organo lithium salts of 4-fluorophenyl methyl sulfone and 5-amino-2-cyano-benzotrifluoride, respectively;

(2) preparation (P2) of the intermediates comprising addition of butyl lithium to a solution of a substrate (S1 or S2 representing 4-fluorophenyl methyl sulfone and 5-amino-2-cyano-benzotrifluoride for (X) and (Y) preparation, respectively) in the organic solvent.

(3) preparation (P3) of methyl 2,3-epoxy-2-methyl propionate comprising addition of methyl methacrylate to oxone dissolved in a basic solution, followed by addition of an acid;

(4) preparation (P4) of 2-hydroxy-2-methyl-3-(4-fluorophenylthio)propionic acid comprising addition of methyl-1,2-epoxy-2-methyl propionate to a solution of 4-fluorothiophenol in methanol, followed by addition of ethyl acetate and recovering the product;

(5) preparation of ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionate comprising addition of ethyl pyruvate to a mixture of 4-fluorophenyl methyl sulfone and butyl lithium in an organic solvent followed by recovering; and

(6) micronized (I) having a mean particle diameter of less than 200 mu m (preferably less than 100 mu m, especially less than 10 mu m).

ACTIVITY - None given in the source material.

MECHANISM OF ACTION - None given in the source material.

USE - Micronized (I) is used for preparation of a composition (claimed) useful for selectively reducing the testosterone level.

ADVANTAGE - The processes are economical, environmentally safe and feasible. The process is simple without involvement of any dangerous oxidizing compounds such as meta-chloroperbenzoic acid. The mean particle size of (I) provides an improved, reproducible and stable dissolution profile. (I) Also has an anti-androgen activity and selectively decreases the testosterone level without influencing the regulation mechanisms of the hypothalamus. (I) (Particularly the (R) isomer) is more active having lesser side effects such as headache and giddiness.

Dwg.0/2

FS CPI
FA AB; DCN
MC CPI: B10-A10; B10-A15; B10-C04B; B14-D02A
TECH UPTX: 20030303
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The basic solution is potassium hydroxide or sodium hydroxide (preferably 10M potassium hydroxide for (P3) and 2N sodium hydroxide for (P4)). Oxone is potassium hydrogen sulfate (KHSO5) (50%). The acid is hydrochloric, nitric or phosphoric acid (preferably 0.05 - 5 N hydrochloric acid).
Preferred Process: In (P1), (i) is added to the mixture at -65 degrees C. (I) Is obtained by evaporating a reaction mixture, preferably separating (i). In (P2), butyl lithium reacts with the substrate in the presence of an anion stabilizer (preferably 1,4-diazabicyclo(2.2.2)octane) at -40 to 10 (preferably -2 to 2) degrees C. In (P3), methyl methacrylate is added in methanol and the oxone solution containing the methyl methacrylate is maintained at pH 6. In (P4), the 4-fluorothiophenol solution is prepared by adding the basic solution under N2 flow. The reaction mixture in (P4) is obtained by stirring at room temperature for 90 minutes. The recovery in (P4) is by extraction (preferably chloroform extraction) and further solidification of the product.
ABEX UPTX: 20030303
SPECIFIC COMPOUNDS - Tetrahydrofuran or diethyl ether are specifically claimed as the organic solvent.

ADMINISTRATION - The dosage of (I) is 2 - 200 (preferably 5 - 100) mg/day and is administered orally or intravenously.

EXAMPLE - 4-Fluorophenyl methyl sulfone (4-FPMS) (5 g) and 1,4-diazabicyclo(2.2.2)octane (3.2 g) (DABCO) were dissolved in tetrahydrofuran (THF) and cooled to -2 degrees C in dry-ice acetone bath. A butyl lithium solution (2.5 M) in hexane (14.5 ml) was added to the cold THF dropwise at -2 to 2 degrees C. The mixture was then stirred for 1 hour and then ethyl pyruvate solution (3.67 g) in THF (30 ml) was added to the mixture at -65 degrees C. The mixture was stirred for 1 hour at -65 to -30 degrees C. 2N hydrochloric acid (HCl) was then added to the reaction and the mixture was warmed to room temperature. The reaction mixture was evaporated in vacuo, after which the residue was extracted with diethyl ether (3 x 100 ml). The combined ether extracts were dried over sodium bisulfate (NaSO4), filtered and purified by column chromatography using dichloromethane to give rac-ethyl-(2-(4-fluorophenyl sulfone))-2-hydroxy propionate.

L92 ANSWER 7 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-339937 [37] WPIX
DNC C2002-097694
TI Preparation of N-phenyl-3-alkyl sulfonyl-2-hydroxy-2-alkylpropanamide derivatives e.g. **bicalutamide**, comprises reaction of substituted benzene and acrylamide derivative, epoxidizing, reacting with thiol and then oxidizing.
DC B05
IN CHEN, B; SUNDEEN, J E; ZHAO, R
PA (CHEN-I) CHEN B; (SUND-I) SUNDEEN J E; (ZHAO-I) ZHAO R; (BRIM) BRISTOL-MYERS SQUIBB CO
CYC 98
PI WO 2002024638 A1 20020328 (200237)* EN 26 C07C317-46
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
US 2002086902 A1 20020704 (200247) C07C317-24
AU 2001095044 A 20020402 (200252) C07C317-46

US 6562994 B2 20030513 (200335) C07C255-00
EP 1322603 A1 20030702 (200344) EN C07C317-46
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
CZ 2003000836 A3 20030813 (200357) C07C317-46
KR 2003048408 A 20030619 (200369) C07C315-02 <--
HU 2003002930 A2 20031229 (200413) C07C317-46
JP 2004509164 W 20040325 (200422) 44 C07C315-02 <--

ADT WO 2002024638 A1 WO 2001-US42171 20010917; US 2002086902 A1 Provisional US 2000-234121P 20000921, US 2001-953759 20010917; AU 2001095044 A AU 2001-95044 20010917; US 6562994 B2 Provisional US 2000-234121P 20000921, US 2001-953759 20010917; EP 1322603 A1 EP 2001-975752 20010917, WO 2001-US42171 20010917; CZ 2003000836 A3 WO 2001-US42171 20010917, CZ 2003-836 20010917; KR 2003048408 A KR 2003-704173 20030321; HU 2003002930 A2 WO 2001-US42171 20010917, HU 2003-2930 20010917; JP 2004509164 W WO 2001-US42171 20010917, JP 2002-529051 20010917

FDT AU 2001095044 A Based on WO 2002024638; EP 1322603 A1 Based on WO 2002024638; CZ 2003000836 A3 Based on WO 2002024638; HU 2003002930 A2 Based on WO 2002024638; JP 2004509164 W Based on WO 2002024638

PRAI US 2000-234121P 20000921; US 2001-953759 20010917

IC ICM C07C255-00; **C07C315-02**; C07C317-24; C07C317-46
ICS A61K031-16; A61K031-277; C07C231-08; C07C253-30; C07C255-60; C07C255-66; **C07C315-00**; C07C317-00; C07C319-14; C07C323-52; C07C323-62; C07D301-14; C07D301-16; C07D303-48

AB WO 200224638 A UPAB: 20020613
NOVELTY - Preparation of an N-(phenyl)-3-alkylsulfonyl-2-hydroxy-2-alkylpropanamide derivative (I) comprises reacting a substituted benzene derivative (II) with an alpha , beta -unsaturated propanamide derivative (III) in the presence of a first base followed by reaction with an epoxidizing agent, then with a thiol derivative in the presence of a second base and then reacting with an oxidizing agent.

DETAILED DESCRIPTION - Preparation of an N-(phenyl)-3-alkylsulfonyl-2-hydroxy-2-alkylpropanamide derivative of formula (I) comprises:

(a) reacting a substituted benzene derivative of formula (II) with an alpha , beta -unsaturated propanamide derivative of formula (III) in the presence of a first base to form an N-(substituted phenyl)- alpha , beta -unsaturated propanamide derivative of formula (IV);

(b) reacting (IV) with an epoxidizing agent to form an epoxide of formula (V);

(c) reacting (V) with a thiol of formula R2SH (VI) in the presence of a second base to form a sulfide of formula (VII); and

(d) reacting (VII) with an oxidizing agent.

Y' = T' or alkylsulfonyl;
T' = cyano, nitro, perfluoroalkyl, alkylcarbonyl or alkoxycarbonyl;
R = T', alkyl or alkoxy;
R1 = (halo)alkyl;
R2 = alkyl or (hetero)aryl;
X = F, Cl, Br, I or OSO2R3; and
R3 = alkyl or aryl.

INDEPENDENT CLAIMS are also included for the following:
(A) preparation of (IV) involving step (a);
(B) preparation of (V) involving steps (a) and (b); and
(C) preparation of (VII) involving steps (a)-(c).

ACTIVITY - Antiandrogenic; cytostatic; dermatological; antiseborrheic; depilatory.

MECHANISM OF ACTION - None given.

USE - For the preparation of an N-(substituted phenyl)-3-alkyl, aryl, or heteroarylsulfonyl-2-hydroxy-2-alkyl or haloalkylpropanamide (e.g. N-(4-cyano-3-trifluoromethyl)phenyl)-3-(4-fluoro-phenyl)sulfonyl)-2-hydroxy-2-methylpropanamide) (**bicalutamide**) (claimed) which are useful in the treatment of malignant or benign prostatic disease or androgen dependent disease conditions such as acne, hirsutism or seborrhosa.

ADVANTAGE - The process does not require the use of chromagraphic separations and uses less expensive starting materials compared to prior art processes. (I) exhibits antiandrogenactivity.
Dwg.0/0
FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B07-H; B10-A10; B10-A15; B10-D03; B14-H01B; B14-N17C; B14-R02
TECH UPTX: 20020613
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The first and second bases are selected from alkali metal hydride, alkali metal alkoxide, alkali metal amide or alkyllithium (preferably sodium hydride, potassium tert-butoxide, sodium amide or butyllithium, especially sodium hydride).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The epoxidizing agent is peracid or dioxirane (preferably peracetic acid, trifluoroperacetic acid or 3-chloroperbenzoic acid, especially trifluoroperacetic acid). The trifluoroacetic acid is formed in situ from hydrogen peroxide or trifluoroacetic anhydride. The oxidizing agent is selected from a peracid, dioxirane, hydrogen peroxide, sodium periodate, N-methylmorphine N-oxide or oxone (preferably peracid). The peracid is peracetic acid, trifluoroperacetic acid or 3-chloroperbenzoic acid (preferably trifluoroperacetic acid).
Preferred Method: Steps (a)-(d) are conducted in the presence of an aprotic solvent selected from halogenated hydrocarbon, hydrocarbon, aromatic hydrocarbon, halogenated aromatic hydrocarbon, ether, ester and/or amide. Step (a) is conducted in the presence of N,N-dimethylformamide. Step (b) is conducted in the presence of dichloromethane. Step (c) is conducted in the presence of tetrahydrofuran. Step (d) is conducted in the presence of dichloromethane.
ABEX UPTX: 20020613
EXAMPLE - To a solution of methacrylamide (153 g) in N,N-dimethyl formamide (800 ml) was added 4-cyano-3-(trifluoromethyl)phenyl fluoride (200 g) at room temperature (RT). The solution was cooled and after work up gave N-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide (A) (260 g). To a stirred solution of (A) (250 g) in dichloromethane (1.2 l) was added 30 % hydrogen peroxide (170 ml). The solution was cooled and after work up gave N-(4-cyano-3-trifluoromethyl)phenyl)methacrylamide epoxide (B) (180 g). To a 0 degrees C mixture of sodium hydride (193 g) in tetrahydrofuran (THF) (333 ml) was added a solution of 4-fluorobenzenethiol (81.8 ml) in THF (248 ml) by maintaining temperature below 25 degrees C during addition. The mixture was stirred for 5 minutes and a solution of (B) (166 g) in THF (830 ml) was added. After work up it gave N-(4-cyano-3-trifluoromethyl)phenyl)-3-((4-fluorophenyl)thio)-2-hydroxy-2-methylpropanamide (C) (244.74 g). To a solution of (C) (244.74 g) in dichloromethane (1.5 L) was added 30 % hydrogen peroxide (141.6 ml), cooled and added trifluoroacetic anhydride (520.6 ml). After work up this gave N-(4-cyano-3-trifluoromethyl)phenyl)-3-(4-fluorophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (**bicalutamide**) (255.2 g; 97 % yield).

DEFINITIONS - Preferred Definitions:
R3 = trifluoromethyl;
Y' = cyano or nitro;
R = trifluoromethyl;
R1 = methyl; and
R2 = 1-4C alkyl, phenyl, p-fluorophenyl, thiazol-2-yl, 4-methylthiazol-2-yl, 5-methyl-1,3,4-thiadiazol-2-yl or 2-pyridyl.

L92 ANSWER 8 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-355089 [37] WPIX
DNC C2001-109964

TI Asymmetric synthesis of enantiomers of acylanalides and/or their intermediates, particularly **bicalutamide**, useful e.g. for treating prostate cancer.

DC B05

IN EKWURIBE, N N; EKWURIBE, N

PA (NOBE-N) NOBEX CORP; (EKWU-I) EKWURIBE N N

CYC 95

PI WO 2001028990 A2 20010426 (200137)* EN 44 C07C315-00 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001019686 A 20010430 (200148) C07C315-00 <--
NO 2002001831 A 20020619 (200253) C07C315-00 <--
EP 1222165 A2 20020717 (200254) EN C07C317-34
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2002001340 A3 20020814 (200263) C07C315-00 <--
BR 2000014889 A 20021231 (200309) C07C315-00 <--
KR 2002091047 A 20021205 (200324) C07C315-00 <--
JP 2003512351 W 20030402 (200325) 53 C07C319-20
HU 2002003785 A2 20030428 (200337) C07C317-34
US 6583306 B1 20030624 (200343) C07C315-00 <--
CN 1409702 A 20030409 (200345) C07C317-34
ZA 2002002947 A 20030923 (200368) 66 C07C000-00
US 2004030130 A1 20040212 (200412) C07D279-12
NZ 518392 A 20040227 (200418) C07C315-00 <--

ADT WO 2001028990 A2 WO 2000-US41233 20001018; AU 2001019686 A AU 2001-19686 20001018; NO 2002001831 A WO 2000-US41233 20001018, NO 2002-1831 20020418; EP 1222165 A2 EP 2000-982690 20001018, WO 2000-US41233 20001018; CZ 2002001340 A3 WO 2000-US41233 20001018, CZ 2002-1340 20001018; BR 2000014889 A BR 2000-14889 20001018, WO 2000-US41233 20001018; KR 2002091047 A KR 2002-704966 20020418; JP 2003512351 W WO 2000-US41233 20001018, JP 2001-531790 20001018; HU 2002003785 A2 WO 2000-US41233 20001018, HU 2002-3785 20001018; US 6583306 B1 Provisional US 1999-160412P 19991019, US 2000-691621 20001018; CN 1409702 A CN 2000-817022 20001018; ZA 2002002947 A ZA 2002-2947 20020415; US 2004030130 A1 Provisional US 1999-160412P 19991019, Div ex US 2000-691621 20001018, US 2003-444343 20030523; NZ 518392 A NZ 2000-518392 20001018, WO 2000-US41233 20001018

FDT AU 2001019686 A Based on WO 2001028990; EP 1222165 A2 Based on WO 2001028990; CZ 2002001340 A3 Based on WO 2001028990; BR 2000014889 A Based on WO 2001028990; JP 2003512351 W Based on WO 2001028990; HU 2002003785 A2 Based on WO 2001028990; US 2004030130 A1 Div ex US 6583306; NZ 518392 A Based on WO 2001028990

PRAI US 1999-160412P 19991019; US 2000-691621 20001018; US 2003-444343 20030523

IC ICM C07C000-00; **C07C315-00**; C07C317-34; C07C319-20; C07D279-12
ICS C07C231-00; C07C255-49; **C07C315-02**; C07C317-14; C07C317-46; C07C319-14; C07C323-52; C07C323-60; C07M007-00

ICA C07B053-00; C07D317-34; C07D498-04

ICI C07M007:00

AB WO 200128990 A UPAB: 20020226
NOVELTY - Enantiomers of acylanilides and/or their intermediates are prepared with improved separation, and the preferred (R)-enantiomer of **bicalutamide** is prepared using (S) citramalic acid as a starting material.

DETAILED DESCRIPTION - Asymmetric synthesis of an enantiomer of an acylanilide, or a derivative, comprises: (a) contacting a compound having a ring structure that, when opened, provides a substituent having the structure (I), with a compound of formula R7-R6-X1-H (II) to give (III);

R1 = 1-4C alkyl or 1-4C haloalkyl;

R2 = 1-6C alkyl;
R3 = CH2OR4;
R4 = H, benzyl, C(O)Me or C(O)OR5;
R5 = H or alkyl;
R6 = a direct link or 1-6C alkyl;
R7 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl; phenyl substituted with 1-3 Q; naphthyl; or Het;
Q = H, halo, NO2, carboxy, carbamoyl or CN; or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulfonyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl, perfluoroalkylsulfonyl, alkoxycarbonyl or N-alkylcarbamoyl, each of 1-4C; or phenyl, phenylthio, phenylsulfinyl or phenylsulfonyl;
Het = a 5-6 membered optionally unsaturated heterocyclic containing 1-3 heteroatoms (O, N or S), which may be a single ring or fused to a benzo-ring; and the heterocyclic is optionally substituted with 1 or 2 halo, CN or NH2, or alkyl, alkoxy, alkylsulfinyl or alkylsulfonyl, each of 1-4C, or oxy or OH, or 1 or 2 oxo substituents;
X1 = O, S, -SO-, -SO2-, -NH- or -NR8-;
R8 = 1-6C alkyl;
X2 = as defined for X1 or -NR8a-;
R8a = oxidized alkylimino;
and (b) treating (III) under suitable conditions to give a pure enantiomer of an acylanilide or derivative.
INDEPENDENT CLAIMS are included for the following: (1) new intermediates of formula (IV) and their preparation;
R9 = H or straight, branched or cyclic alkyl;
R10 = alkyl, aryl or R11X43;
R11 = alkyl;
X4 = alkyl, halo or aryl;
X3 = a leaving group;
and (2) preparation of optically active compounds (III); (3) preparation of a pure enantiomer of an acylanilide or derivative of formula (XIVA) from citramalic acid by the following reaction scheme:
(i) aldol condensation with citramalic acid (X) to give (XV);
(ii) decarboxylating (XV) to give (IVA);
(iii) hydrolyzing (IVA) to give (XXIII);
(iv) treating (XXIII) with (II) to give (XVIII);
(v) treating (XVIII) with (XIII);
(vi) oxidizing the product from (v) to give (XIVA).
R14 = CN, carbamoyl, NO2, F, Cl, Br or I; or alkanoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulfinyl or perfluoroalkylsulfonyl each having 1-4C; or phenylthio, phenylsulfinyl or phenylsulfonyl;
R13 = R14, H, 1-4C alkyl or 1-4C alkoxy; and
R15 = H or halo.
ACTIVITY - Anticancer.
MECHANISM OF ACTION - None given
USE - The acylanilide bicalutamide (N-(4-cyano-3 (trifluoromethyl)phenyl)-3-((4-fluorophenyl)sulfonyl)-2-hydroxy-2 methyl-propanamide) (particularly R-enantiomer) is useful for treating androgen-dependent diseases, e.g. prostate cancer.
ADVANTAGE - The asymmetric methods are more cost effective than conventional methods, and do not require use of the expensive (R) proline as in previous methods.
Dwg.0/3

FS CPI
FA AB; GI; DCN
MC CPI: B10-D03; B14-H01
TECH UPTX: 20010704
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Methods: The compound having a ring structure is of formula (IV), (VIII) or (XI), and reacts with (II) to form (V), (IX) or (XII) respectively.
X5 = a leaving group.

Compound (V), (IX) or (XII) is reacted to form (III).
In step (b), (III) is treated with a compound of formula (XIII) to form acylanilide (XIV):
Preferred Preparation of (XIVA): Step (i) is carried out with bromal in the presence of sulfuric acid. In step (ii) decarboxylation is carried out by decarboxylatively brominating with 2-mercaptoyridine N-oxide, dicyclohexylcarbodiamide and CBrCl3. In step (iii) hydrolysis is carried out with HCl. In step (iv), (II) is 4-fluorobenzenethiol, and in step (v), (XVIII) is reacted with thionyl chloride to give the acid chloride, then reacted with 4-amino-2-trifluoromethylbenzonitrile. Oxidation in step (vi) is carried out with meta-chloroperbenzoic acid. (S) Citramalic acid produces (R)-**bicalutamide**, and (R)-citramalic acid produces the (S)-enantiomer.

ABEX UPTX: 20010704
SPECIFIC COMPOUNDS - 5-Bromomethyl-5-methyl-2-tribromomethyl (1,3)dioxolan-4-one (IVa) is specifically claimed.
EXAMPLE - Bromal (89.1 mmol) and (S)-citramalic acid (74.2 mmol) were cooled to 0degreesC under an inert atmosphere, and sulfuric acid (25 ml) was added dropwise with stirring. After 2 hours, cooling was removed and the mixture was stirred overnight at room temperature. The solution was diluted with ice and extracted repeatedly with ethyl acetate. The organic layer was back extracted with water, dried and filtered. The filtrate was concentrated, and **crystallization** from toluene/hexanes gave 4 methyl-5-oxo-2-tribromomethyl-(1,31-dioxolan-4-yl)-acetic acid (60% yield).
This compound and 2-mercaptopyridine N-oxide were suspended in CBrCl3, and refluxed. A solution of dicyclohexylcarbodiamide in CBrCl3 was added slowly over 30 minutes. After stirring for 1 hour, the product was purified by silica gel chromatography to give (IVa) (65% yield), m.pt. 110-113degreesC.
(IVa) was dissolved in a mixture of isopropanol:1M NaOH (1:1). After 3 hours, 4-fluorobenzenethiol was added, and the mixture was stirred overnight. pH was adjusted to 8 and the mixture was extracted with CH2Cl2. Work up and **recrystallization** from CHCl3/petroleum ether gave 3-(4-fluoro phenylsulfanyl)-2-hydroxy-2-methyl-propionic acid. (80% yield), m.pt. 73-75degreesC.
The hydroxyacid (8.5 mmol) and 4-amino-2 trifluoromethylbenzonitrile (11 mmol) were dissolved in dry dimethylacetamide (15 ml) under an inert atmosphere. The solution was cooled to -10degreesC, and thionyl chloride (10 mmol) was added slowly. The mixture was stirred for 15 minutes at -10degreesC, and overnight at room temperature, then diluted with CH2Cl2 and extracted with saturated NaHCO3. Work up and purification by silica gel chromatography gave N-(4-cyano-3-trifluoromethyl phenyl)-3-(4-fluoro-phenylsulfanyl)-2-hydroxy-2-methyl propionamide (45%).
This compound (3.19 mmol) was dissolved in CH2Cl2 (43 ml) and meta-chloroperbenzoic acid (9.57 mmol) was added. After stirring overnight at room temperature, the mixture was diluted with ethyl acetate and extracted with Na2SO3 and NaHCO3. Work up and purification by silica gel chromatography gave **bicalutamide** (94% yield), m.pt. 178degreesC.

L92 ANSWER 9 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-343585 [36] WPIX
DNC C2001-106402
TI Resolution of intermediates useful in synthesis of acylanilide compounds, e.g., the anticancer agent **bicalutamide**, especially by resolving a cinchonidine salt by **crystallization.**
DC B05
IN EKWURIBE, N N; JAMES, K D; RAJAGOPALAN, J
PA (NOBE-N) NOBEX CORP
CYC 95
PI WO 2001034563 A1 20010517 (200136)* EN 27 C07C315-06 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

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|---|---|---|---|---|---|---|---|
| AU | 2001026195 | A | 20010606 | (200152) | | C07C315-06 | <-- |
| BR | 2000015124 | A | 20020702 | (200252) | | C07C315-06 | <-- |
| NO | 2002001999 | A | 20020620 | (200253) | | C07C000-00 | |
| EP | 1224167 | A1 | 20020724 | (200256) | EN | C07C315-06 | <-- |

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI

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| CZ | 2002001434 | A3 | 20021113 | (200282) | | C07C315-06 | <-- |
| KR | 2002067509 | A | 20020822 | (200310) | | C07C315-06 | <-- |
| HU | 2002003186 | A2 | 20030128 | (200323) | | C07C315-06 | <-- |
| JP | 2003513955 | W | 20030415 | (200328) | 30 | C07B057-00 | |
| CN | 1413188 | A | 20030423 | (200347) | | C07C315-06 | <-- |
| US | 6593492 | B1 | 20030715 | (200348) | | C07C067-02 | |
| ZA | 2002003228 | A | 20030923 | (200368) | 45 | C07C000-00 | |
| MX | 2002004225 | A1 | 20021001 | (200370) | | C07C315-06 | <-- |
| NZ | 518552 | A | 20031031 | (200380) | | C07C315-06 | <-- |

ADT WO 2001034563 A1 WO 2000-US41609 20001025; AU 2001026195 A AU 2001-26195 20001025; BR 2000015124 A BR 2000-15124 20001025, WO 2000-US41609 20001025; NO 2002001999 A WO 2000-US41609 20001025, NO 2002-1999 20020426; EP 1224167 A1 EP 2000-989719 20001025, WO 2000-US41609 20001025; CZ 2002001434 A3 WO 2000-US41609 20001025, CZ 2002-1434 20001025; KR 2002067509 A KR 2002-705357 20020426; HU 2002003186 A2 WO 2000-US41609 20001025, HU 2002-3186 20001025; JP 2003513955 W WO 2000-US41609 20001025, JP 2001-536512 20001025; CN 1413188 A CN 2000-817760 20001025; US 6593492 B1 Provisional US 1999-161884P 19991027, US 2000-695884 20001025; ZA 2002003228 A ZA 2002-3228 20020423; MX 2002004225 A1 WO 2000-US41609 20001025, MX 2002-4225 20020426; NZ 518552 A NZ 2000-518552 20001025, WO 2000-US41609 20001025

FDT AU 2001026195 A Based on WO 2001034563; BR 2000015124 A Based on WO 2001034563; EP 1224167 A1 Based on WO 2001034563; CZ 2002001434 A3 Based on WO 2001034563; HU 2002003186 A2 Based on WO 2001034563; JP 2003513955 W Based on WO 2001034563; MX 2002004225 A1 Based on WO 2001034563; NZ 518552 A Based on WO 2001034563

PRAI US 1999-161884P 19991027; US 2000-695884 20001025

IC ICM C07B057-00; C07C000-00; C07C067-02; **C07C315-06**
ICS **C07C315-04**; C07C317-28; C07C317-46

AB WO 200134563 A UPAB: 20010628

NOVELTY - A pure enantiomer of an acylanilide is prepared by:

(a) resolving an intermediate (I); and

(b) treating the resolved intermediate (I) under conditions sufficient to give a pure enantiomer of an acylanilide.

DETAILED DESCRIPTION - Preparation of a pure enantiomer of an acylanilide comprises:

(a) resolving an intermediate compound of formula (I); and

(b) treating the resolved intermediate (I) under conditions sufficient to give a pure enantiomer of an acylanilide.

R1 = T' or 1-4C haloalkyl;

R2 = 1-6C alkylene;

R3 = 1-6C alkylene, or a bond;

R4 = 1-6C alkyl, 2-6C alkenyl, 1-6C hydroxyalkyl or 3-6C cycloalkyl; Ph (optionally substituted by 1-3 halo, NO2, carboxy, carbamoyl, CN, T', T'O, 1-4C alkanoyl, T'S, T'SO, T'SO2, Q, QS, QSO, QSO2, T'OOC, CONHT', Ph, PhS, PhSO or PhSO2); naphthyl; or Het (optionally substituted by 1-2 halo, CN, amino, T', T'S, T'SO, T'SO2, oxy or hydroxy substituents, or (if sufficiently saturated) 1-2 oxo substituents);

X1 = O, S, SO, SO2, NH or NR5;

R5 = 1-6C alkyl;

T', Q = 1-4C alkyl and 1-4C perfluoroalkyl respectively;

Ph = phenyl; and

Het = a 5-6 membered saturated or unsaturated heterocycle which

contains 1-3 O, N and/or S atoms and which is optionally fused to a benzo ring.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - None given.

USE - The process is useful for production of pure enantiomers of acylanilide compounds, especially **bicalutamide**, which is useful in treatment of prostate cancer.

ADVANTAGE - The process allows resolution of enantiomers of intermediate compounds before reaction with expensive materials which introduce other portions to the final molecule. This means that these expensive materials are not used in production of inactive enantiomers which will be discarded. The process thus allows more cost effective production of materials such as **bicalutamide.**

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: B06-H; B07-H; B10-A10; B10-A15; B10-D03; B14-H01B

TECH UPTX: 20010628

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred process: the resolution step comprises resolving the intermediate compound of formula (I) by **crystallization** or high performance liquid chromatography. Resolution by **crystallization** comprises contacting (I) with a chiral base to give a diastereomeric mixture of a chiral salt, resolving the mixture by **crystallization** and recovering a pure enantiomer of (I). The chiral base is especially (-)-cinchonidine. The solvent system used for resolution by **crystallization** is especially a mixture of methylene chloride and diethyl ether, most especially a mixture of 1-40 volume % of methylene chloride and 60-99 vol. % of diethyl ether. For production of **bicalutamide**, an intermediate compound (I; R1 = Me, R2 = CH2, R3 = a bond, R4 = 4-fluorophenyl and X1 = SO2) is resolved as outlined above, then the resolved compound can be reacted with a compound of formula (II) to give a pure enantiomer of **bicalutamide**

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R7 = perfluoroalkyl.

ABEX UPTX: 20010628

EXAMPLE - In a typical process, the salt of an (R,S)-hydroxyacid and (-)-cinchonidine was formed by mixing a solution of the hydroxyacid (1 equivalent) with a solution of (-)-cinchonidine (1 equivalent). The cinchonidine was typically dissolved in chloroform while the acid was dissolved in, e.g., chloroform, methylene chloride, ethyl acetate or ethanol. The mixture was then stirred at room temperature overnight. The solvent was then removed by rotary evaporation. The salt (typically 20 mg) was then placed in a vial and treated with ethyl ether (2 ml). Methylene chloride was then added, with shaking, until all of the salt had been solubilized. The solution was then placed at 4 degrees C for **crystallization.** After **crystallization**, the supernatant was removed. The **crystals** were then dissolved in deuterated chloroform. The ratio of (R)- to (S)-enantiomer could then be assayed by integration of the fluorine signal using 19F NMR.

L92 ANSWER 10 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-102880 [11] WPIX

DNC C2001-030165

TI Synthesis of **bicalutamide**, a selective anti-androgen, involves the oxidation of its thioether precursor.

DC B05

IN BOR, A; BRLIK, J; DEMETER, A; GALIK, G; HORVATH, J; SOEROES, B; TRISCHLER, F; TUBA, Z

PA (RICT) RICHTER GEDEON VEGYESZETI GYAR

CYC 94

PI WO 2001000608 A1 20010104 (200111)* EN 33 C07D327-10

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000052397 A 20010131 (200124)
HU 9901937 A1 20010428 (200131) C07C317-32
EP 1189898 A1 20020327 (200229) EN C07D327-10
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI
EP 1189898 B1 20030312 (200319) EN C07D327-10
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 60001657 E 20030417 (200333) C07D327-10
ES 2188550 T3 20030701 (200347) C07D327-10

ADT WO 2001000608 A1 WO 2000-HU49 20000526; AU 2000052397 A AU 2000-52397 20000526; HU 9901937 A1 HU 1999-1937 19990610; EP 1189898 A1 EP 2000-937111 20000526, WO 2000-HU49 20000526; EP 1189898 B1 EP 2000-937111 20000526, WO 2000-HU49 20000526; DE 60001657 E DE 2000-00001657 20000526, EP 2000-937111 20000526, WO 2000-HU49 20000526; ES 2188550 T3 EP 2000-937111 20000526

FDT AU 2000052397 A Based on WO 2001000608; EP 1189898 A1 Based on WO 2001000608; EP 1189898 B1 Based on WO 2001000608; DE 60001657 E Based on EP 1189898, Based on WO 2001000608; ES 2188550 T3 Based on EP 1189898

PRAI HU 1999-1937 19990610

IC ICM C07C317-32; C07D327-10
ICS C07C253-30; C07C303-28; C07C309-66; **C07C315-02**; C07C317-46; C07C319-14; C07C323-60

AB WO 200100608 A UPAB: 20010224

NOVELTY - A multistep process for making optically pure enantiomers of **bicalutamide** (I) involving the oxidation of the precursor thioether (II) is new.

DETAILED DESCRIPTION - A process for making racemic or optically pure R(-) or S(+) **bicalutamide** (I) comprises:

(1) reacting racemic or optically pure 2,3-dihydroxy-2-methyl-propionic acid (VII) with thionyl chloride in a halohydrocarbon or in an aromatic solvent with an aromatic amine base;

(2) reacting the resulting 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one (VI) with 4-cyano-3 trifluoromethylaniline in an inert solvent with a tertiary amine at between 0 and -40 deg. C;

(3) hydrolyzing the resulting 4-((4-cyano-3-(trifluoromethyl)-anilino)-carbonyl)-4-methyl-1,3,2-dioxathiolanone-2-one (V) under aqueous basic conditions;

(4) sulfonating the N-(4-cyano-3-(trifluoromethyl)-phenyl)-2,3-dihydroxy-2-methyl-propionamide (IV) with a sulfonyl halogenide RSO2X in a halohydrocarbon solvent in the presence of a tertiary amine base;

(5) reacting the resulting sulfonic ester (III) with 4-fluorophenol in the presence of a base; and

(6) oxidizing the thioether (II) with

(a) an inorganic peroxy salt in a solvent/water mixture optionally (for solvents immiscible in water) in the presence of a transfer catalyst, or

(b) aqueous hydrogen peroxide

(1) in a 1-4C aliphatic carboxylic acid,

(2) under aqueous basic conditions with a water-miscible organic solvent, or

(3) in an water-immiscible organic solvent in the presence of a phase transfer catalyst and a vanadium or chromium salt.

R = methyl, p-tolyl or p-bromophenyl; and

X = halo.

ACTIVITY - Anti-androgen.

USE - Useful for making **bicalutamide** with selective anti-androgen activity.

ADVANTAGE - The starting material, available cheaply, allows the production of pure enantiomers. Oxidative steps are safe and do not cause

environmental pollution. The use of inflammable sodium hydride is avoided. The use of harmful reagents such as potassium cyanide in acidic medium are avoided. No special equipment is needed for commercial manufacture e.g. acid-resistant autoclaves. Product is pure enough to only require simple purification methods to make the final product. Existing processes require the separation of the optically pure enantiomers from a racemic mix leading to high levels of wastage. Whereas the new method allows more of the starting materials to be converted into find optically pure enantiomer with less waste.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B05-A01A; B05-A01B; B05-A03B; B07-C; B07-D04C; B10-A04; B10-A09C; B10-A10; B10-A15; B10-A22; B10-B04A; B10-B04B; B10-C04D; B10-C04E; B10-E02; B10-E04D; B10-H02F; B10-J02; B11-C01; B14-D02A

TECH UPTX: 20010224

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Synthesis:

(1) Halohydrocarbon is selected from dichloromethane, chloroform or 1,2-dichloroethane. The aromatic solvent is benzene, toluene or xylene. The aromatic base is pyridine.

(2) The tertiary amine base is triethylamine. The inert solvent is halohydrocarbon, aromatic hydrocarbon or an ether. The reaction is carried out between 0degreesC and -15degreesC.

(3) Aqueous alkali metal hydroxide makes aqueous basic conditions.

(4) The halohydrocarbon solvent is dichloromethane and the tertiary amine base is pyridine.

(5) The base is sodium hydroxide in isopropanol.

(6) The inorganic peroxy salt is a mixture of 2KHSO5KHSO4 K2SO4 (Oxone ). The solvent mix is methanol and water, dichloromethane or ethyl acetate and water with a phase transfer catalyst. The preferred carboxylic acids are formic and acetic acid. Optionally (II) is oxidized in a basic medium of aqueous alkali metal carbonate solution with acetonitrile and/or 1-4C alkanol (preferably methanol) as a water-miscible solvent with hydrogen peroxide; or in dichloromethane with water in the presence of a quaternary ammonium salt as a phase transfer catalyst with sodium tungstate and aqueous hydrogen peroxide. The phase transfer catalyst is tetrabutylammonium hydrogensulfate, cetylammonium chloride or tetrabutylammonium chloride.

ABEX UPTX: 20010224

SPECIFIC COMPOUNDS - The use of Oxone as an inorganic peroxy salt, tetrabutylammonium hydrogensulfate and 2 other phase transfer catalysts are specifically claimed.

EXAMPLE - A mix of (VII) (75g) in toluene (2 Liters) and pyridine (1.5ml) was cooled to 10degreesC before adding thionyl chloride (1.524mol) and refluxing for 4 hours before concentrating under reduced pressure and distilling in vacuum to make (VI). A solution of 4-cyano-3-trifluoromethylaniline (44g) in dichloromethane (880ml) was mixed with triethylamine (90ml) before cooling to -15degreesC and adding (VI) (64ml) dropwise. The reaction was stirred at 0degreesC for 3 hours before extraction with 10% hydrochloric acid (500ml), drying the organic layer over sodium sulfate and concentrating under reduced pressure. The residue (V) was dissolved in tetrahydrofuran (1L) and 10% sodium hydroxide (440ml) at 10degreesC. After mixing for 0.5 hours the pH was titrated to 2 with concentrated hydrochloric acid the solution was evaporated to 100ml and the residue was dissolved in ethyl acetate (to make 260ml), treated with charcoal, and filtered before adding petroleum ether (520ml). The precipitated **crystals** (IV) were filtered and dried at 60degreesC in a vacuum. A solution of (IV) (5g) in dry pyridine (50ml) at 0C was mixed with 4-bromo-benzene sulfonyl chloride (8.86g) for 5 hours before diluting with dichloromethane (200ml), washing 3 times in saturated aqueous sodium bicarbonate (50ml), twice with 10% aqueous hydrochloric acid (50ml) and in brine (50ml). The organic layer was dried over sodium sulfate, concentrated under vacuum, and the residue was

**crystallized** in 1 part ethylacetate/ 5 parts petroleum ether to give (III). 4-Fluorothiophenol (25.6g) in isopropanol (500ml) was mixed with sodium hydroxide (8.4g) in water (400ml) under nitrogen for 2 hours before adding (III) (58.6g) in isopropanol (500ml) and mixing for another 5 hours. The mix was titrated to pH7 with concentrated hydrochloric acid before treatment with charcoal at reflux temperature. After evaporating most of the isopropanol under vacuum, 2% aqueous sodium hydroxide (250ml) was added and stirred before filtering and washing of the settled **crystals.** The dried **crystals** (II) were **recrystallized** as above. A solution of (II) (52g) in acetic acid (520ml) at 10degreesC was mixed with 30% aqueous hydrogen peroxide (156ml) overnight before adding saturated aqueous sodium bicarbonate (3L) and extracting 3 times with dichloromethane (500ml). The combined organic layers were washed with brine (500ml) before drying over sodium sulfate and concentrating under reduced pressure. The residue was dissolved in ethyl acetate (500ml), cooled to 5degreesC and was mixed with petroleum ether (2L). The precipitated **crystals** were filtered, washed with petroleum ether (40ml), cooled to 0degreesC and dried at 60degreesC in a vacuum to make **bicalutamide** (47.25g: yield 84.15%).

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